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# NOMA

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During recent decades there have been relatively few reports of cases of noma, and the older generation of physicians have observed but a limited number. The few records that appear in the literature are chiefly case reports. Textbooks still rely largely on descriptions given by older authors, which usually date back at least fifty years.

In my late service as head of the academic children's clinic at Düsseldorf I saw but a single case of noma in ten years' experience, and in this case the disease was subsequent to measles. The absence of the condition in such a quantity of material as was there available made me minimize the importance of the disease in the practice of pediatrics. During my present service of three years I have, therefore, been astonished to have been able to observe no less than 40 cases of noma in the clinic of the Children's Hospital. Of these, 22 cases came under observation during 1938 alone. All the patients came from the vicinity of Ankara, 3 from the city itself. Moreover, numbers of Turkish physicians have informed me that the disease is anything but rare in this country and that it is especially prevalent in some districts and in some years. Exact data on the epidemiology of the disease are, however, unobtainable. It is nevertheless obvious that noma constitutes one of the important and as yet unsolved problems of Turkey.

The seasonal distribution of the 40 cases viewed by my associates and me in our hospital during the years 1936 to 1938 inclusive is shown in the tabulation:

*Monthly Incidence of Forty Cases of Noma Observed in Three Years*

| Month | No. of Cases | Month | No. of Cases |
|---|---|---|---|
| January | 2 | July | 3 |
| February | 2 | August | 9 |
| March | 1 | September | 5 |
| April | 1 | October | 6 |
| May | 1 | November | 5 |
| June | 2 | December | 3 |

It is seen that in the majority of cases the disease occurred during the months from August to November, inclusive, which constitute the

hot season in this country. However at least 1 case was encountered in each month. It is interesting that the seasonal disposition is precisely similar to that of malaria in this area, especially that of the estivo-autumnal variety. Indeed, this intimate connection of noma and malaria has attracted my attention, since of the 22 cases observed during 1938 in 19 plasmodia were demonstrable in the blood or spleen (in 18 cases in the peripheral blood and in 1 in the spleen). In 16 cases the parasite found was Plasmodium falciparum, in 1 Plasmodium vivax and in 1 infection with all three plasmodia.

In two patients noma was preceded by an attack of typhoid fever. With 1 other exception no other infectious disease could be associated with the appearance of noma.

Postmortem examinations made during 1936 and 1937 showed intense deposits of pigment in various tissues—a characteristic sign of chronic malaria. During those first two years my associates and I unfortunately neglected to examine the blood for plasmodia because the temperature curves of the patients had never suggested malaria. In most of the cases noma progressed without fever, the temperature varying only between 36 and 37 C. (96.8 and 98.6 F.) even in those exhibiting extensive destruction of the facial tissues. The temperature variations may be summarized more precisely as follows:

*Temperature Variations in Forty Cases of Noma*

| No. of Cases | Temperature | |
|---|---|---|
| | C. | F. |
| 26 | 36 -37 | 96.8- 98.6 |
| 7 | 37.1-38 | 98.8-100.4 |
| 5 | 38.1-39 | 100.6-102.2 |
| 2 | 39.1-40 | 102.4-104 |

On the other hand, the pulse rate was generally high, varying from 120 to 140 per minute even in those having little or no fever. In a few cases the rate varied from 80 to 100 per minute.

The general bodily condition of the patients, with but few exceptions, was good (fig. 1). In a few of the cases the patients who came to the hospital late poor care and poor nourishment at home were factors causing cachexia. In the patients seen early, on the contrary, in contrast to the classic descriptions, the general state was good. According to our observations the condition is by no means limited to the cachectic, or poorly nourished.

Our observations also indicate that in this country certain infectious diseases, especially malaria, are perhaps important factors in predisposing a person to an attack of noma by lowering the natural resistance of the organism.

Regarding the clinical picture of noma I have nothing to add to the classic descriptions. The fact that the patient constantly feels well despite the extremely destructive process going on in the face is enough to indicate that no general intoxication exists and that the process of intoxication remains strictly local, leading to necrobiosis in the affected part. It is true, however, that general prostration and drowsiness shortly precede death.

Good appetite and the absence of pain are paradoxic to the severity of the disease. In only 4 of our patients were there any early signs of general intoxication. These were all between 2 and 5 years of age. One of them died in such an early stage of the disease that there had

Fig. 1.—Noma in a 5 year old girl. The patient is strong and well nourished.

not been time for any considerable necrosis to take place. To account for the intoxication in these cases there could be found nothing at autopsy except simple pulmonary emphysema.

The absence of a strong leukocytic reaction is also of interest, as it has not been pointed out by other writers. In our cases the average white blood cell counts were as follows:

*White Cell Counts in Forty Cases of Noma*

| No. of Cases | White Cells per Cu. Mm. |
|---|---|
| 5 | 6,000- 7,000 |
| 12 | 7,000- 8,000 |
| 5 | 8,000- 9,000 |
| 6 | 9,000-10,000 |
| 5 | 10,000-12,000 |
| 4 | 12,000-15,000 |
| 3 | 15,000-20,000 |

In 28 of the 40 patients an average of 10,000 white cells per cubic millimeter was not exceeded. The differential count always showed a relative increase of polymorphonuclear cells with a typical deviation to the left. This absence of a marked leukocytic reaction is another indication confirming my belief that noma is preponderantly a local infection. Even at the site of involvement histologic examination showed little if any leukocytic response. One can thus reasonably maintain that as necrobiosis progresses in noma there is no remarkable response on the part of the leukocytic system.

With a protracted course a rise of temperature indicating general septicemia and, in many cases, also gangrenous pneumonia were observed a few days before death. This septicemia begins with and is due to thrombosis of the blood vessels of the affected area. In postmortem dissections numerous emboli of bacteria, chiefly in the spleen, were demonstrable. I regard the gangrenous pneumonia as primarily aspiratory in origin. Neither of these complications, however, has more than secondary importance to the main problem of noma.

The age distribution in our cases was as follows:

*Age Distribution in Forty Cases of Noma*

| Age, Yr. | No. of Cases | Age, Yr. | No. of Cases |
|---|---|---|---|
| 0-1 | 0 | 7- 8 | 1 |
| 1-2 | 6 | 8- 9 | 2 |
| 2-3 | 3 | 9-10 | 0 |
| 3-4 | 9 | 10-11 | 1 |
| 4-5 | 7 | 11-12 | 1 |
| 5-6 | 5 | 20 and over | 2 |
| 6-7 | 3 | | |

It is seen that, as other writers have pointed out, noma is a disease of young children. With the exception of 2 patients whose ages were 20 and 35 years, respectively, all were under 12 years of age.

Ten of our patients were girls, 2 were women, and the remainder were boys. This does not agree with the theory of predilection for the female sex commonly referred to in the literature.

There is still ignorance of the exact causes of noma. It appears, however, that, aside from the action of the specific virus or agent, the diminished resistance induced by preceding infectious diseases and their noxae, leading to necrobiosis and sometimes death, must play an important role in the disease.

In western Europe the chief predisposing ailment appears to be measles. Among our cases only 1 child had measles before noma, and even in this case the patient was simultaneously suffering from malaria. According to our experience malaria is the usual precursor of noma. I

am inclined to believe that the heavy involvement of the reticuloendothelial system in chronic malaria is one of the reasons for the loss of inherent immunity which leads, under certain conditions, to noma. Noma following typhoid fever, such as we encountered in 2 cases, can also be explained.

In the modern literature avitaminosis is also often referred to as a possible cause of noma. To this theory my experience lends no support. In the majority of cases the disease occurs during the summer and autumn, when the people in this country have the most abundant supplies of vitamins. Furthermore, in our patients there were no symptoms suggesting vitamin deficiency. Finally, no 2 members of the same family living under identical conditions of nutrition were found to have noma.

Seifert [1] recently suggested, in his work "Zur Krankheitsauffassung der Noma und gleichartiger Formen des Gewebsbrandes," a relation between noma and monocytic angina. His observations were based on 3 cases, in 2 of which there was typical agranulocytosis and in the third leukemia. All were characterized by a necrotic process in the mucous membranes in the mouth. Seifert stated the belief that myelophthisis is the cause of noma as well as of other related diseases. Routine examination of the blood in our cases did not support this hypothesis. I believe that necrosis accompanying leukemia or agranulocytosis is not necessarily true noma. The few instances in which true noma and myelophthisis have occurred together appear to me not to surpass the possibilities of pure chance and in any case are too few to permit any conclusion. Further points in support of my thesis are the absence of agranulocytosis or leukemia in my collection of cases of noma and the occurrence of the two conditions without necrosis of the oral mucosa in many cases.

I now approach the most difficult problem, that of the specificity of the virus. Observations in the literature are widely variable in regard to this point. Owing to the infrequency of noma in many countries, many writers have maintained the ideas of tradition. Fischl (1931), in the most extensive work on noma of recent years, maintained no personal point of view on the matter. He referred to the German literature (Schmorl, Pertes, Hofmann, Küster), in which a species of Cladothrix is regarded as the cause. This organism has a close resemblance to the causal organism of "calf diphtheria." It was also described by Flügge as Bacillus necrophorus and by Bang as "Necrosisbacillus." According to Lehmann and Neumann [2] the virus is strictly anaerobic, growing best

1. Seifert, E.: Zentralbl. f. Chir. **65**:738, 1938.

2. Lehmann, K. B., and Neumann, R.: Atlas und Grundriss der Bakteriologie und Lehrbuch der speciellen bakteriologischen Diagnostik, ed. 2, Munich, J. F. Lehmann, 1899.

on blood agar and blood serum agar mediums. Morphologically the organism is inadequately described, however. In the French literature Hutinel and Nobecourt have pointed out the symbiosis of the fusiform bacillus with spirillum. Recently certain German writers (Aschoff, Kumer [3] and Mühlens and associates [4]) have also agreed that this symbiosis, called the Plaut-Vincent symbiosis, probably involves the noma virus. For example, Mühlens and co-workers, in their manual of tropical diseases,[4] illustrate a pure culture of the organisms in this symbiosis obtained from a patient with noma.

It must be obvious that all micro-organisms to be found in the mouth in normal or in pathologic conditions can be demonstrated in the necrotic tissue of noma. It is therefore difficult to determine which of the organisms present is the true cause of the disease. The bacterial flora in all of our 4 cases has been carefully examined. Furthermore, I have submitted smears as well as tissue excised post mortem for bacteriologic examination to Dr. Ali Korur, Director of the Department of Bacteriology in the Children's Hospital, as well as to Professor Gotschlich, Director of the Central Institute of Public Health at Ankara, and to Professor Braun, Director of the Institute of Bacteriology of the University of Istanbul. The results of the examinations of fresh preparations and of cultures were not identical. Fusiform bacilli and spirilla were demonstrated in material from some patients in enormous numbers, while in that of others they were almost completely absent. Even material from the same patients would frequently show great variations in the numbers of different organisms present from day to day. It was possible to demonstrate varying numbers of other organisms as well, including hemolytic streptococci, gram-negative bacilli, diphtheroid bacilli (proved by subsequent culture not to be true diphtheria bacilli), gram-positive and gram-negative cocci, Bacillus coli, Bacillus paracoli idolicum, Bacillus mycoides, Bacillus subtilis and thread bacteria. Thus in my observations I have faced the same difficulties experienced by others in judging the importance of the different organisms in the development of noma.

In the last 12 cases of my series I adopted a new method of procedure, which led to some interesting results. The apparently healthy tissue was pricked just beyond the necrotic parts and a fluid was obtained with a capillary tube. Microscopic examination of this fluid in each case showed fusiform bacilli, spirilla and a few leukocytes without other organisms. The microscopic preparations were identical with

3. Kumer, in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1933, vol. 3.

4. Mühlens, P.; Nauck, E.; Vogel, H., and Ruge, H.: Krankheiten und Hygiene der warmen Länder, ed. 4, Leipzig, Georg Thieme, 1938.

those of Mühlens in his manual. After observing the Plaut-Vincent symbiosis with huge numbers of organisms in the boundary zone in our cases of noma and lacking other exact knowledge concerning the causal factor of the disease, I too agree that this symbiosis probably has a close connection and an important role in the pathogenesis of noma. However, the importance of diminished bodily resistance cannot be denied, as the same symbiosis is also met with in other conditions, such as stomatitis ulcerosa, as well as in the oral cavities of healthy persons.

Among the morbid anatomic features already considered I stressed toxic pulmonary emphysema. In addition I observed varying degrees of fatty degeneration of the liver, swelling of the spleen and some parenchymatous degeneration in the kidneys. Finally, I occasionally noted small areas of necrotic pneumonia.

Because of the paucity of reports on histologic details of noma in modern literature and because my data disagree with the descriptions commonly given in texts and handbooks, the following case observations may be pertinent.[5]

CASE 4.—Gram Stain: A thick ring of bacteria surrounded the hair follicles and small blood vessels. The whole tissue was necrotic and filled with enormous numbers of bacteria. Extensive hemorrhages were scattered diffusely in the tissues, and there were large deposits of blood pigment. Under oil immersion there were seen numerous stained cocci forming chains as well as many bacilli of varying thickness and length. The collection of bacteria formed a thin line about the deposits of pigment. In the necrotic fatty tissue the cocci collected into relatively large masses.

CASE 24.—Smear Preparation (fresh fluid obtained from apparently healthy tissue surrounding the noma): Great numbers of spirilla and fusiform bacilli forming a mesh occupied the whole field of vision (fig. 2).

CASE 19.—Liver: There were irregular scattered large droplets of fat, with no inflammatory infiltrations and no necrosis. There were enlargement and swelling of the Kupffer cells, which were loaded with red blood cells. There was vacuolation of some of the Kupffer cells (fig. 3).

CASE 19.—Spleen: The follicles were small and about some of the central arteries hyaline. The reticulum was heavily loaded with brown pigment. Many of the reticular cells contained enlarged polymorphonuclear cells. Phagocytosis was not obvious (fig. 4).

CASE 4.—Wall of Necrosed Tissue: At the edge the epidermal cells still retained their nuclei. In stroma cells of the corium there were pyknotic nuclei. In the malpighian layer a few cells were vacuolated. As the necrosed tissue was approached more of the epidermal cells had lost their nuclei. This holds true for the dermal cells. At the boundary of the ulceration all nuclei had disappeared

5. Dr. Kamile Aygin, pathologist of the Model Hospital, and Professor Oberndorfer, Director of the Institute of Experimental Pathology of the University of Istanbul, examined the greater number of the histologic preparations.

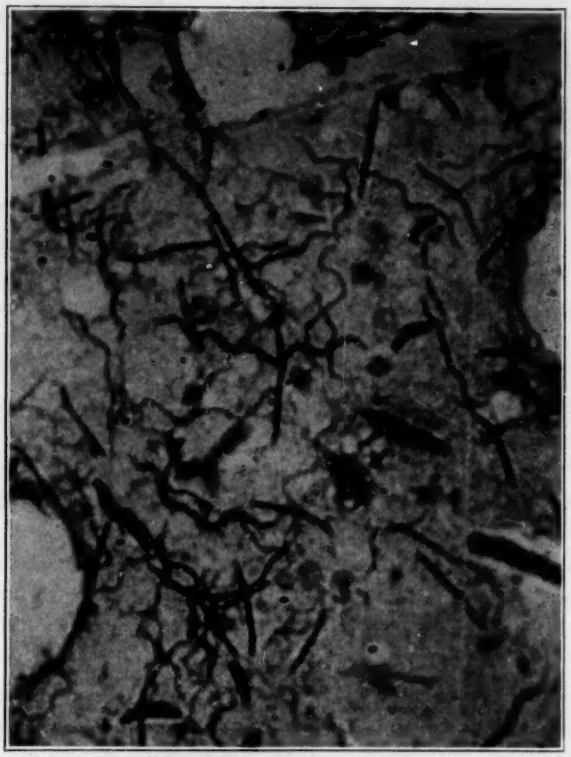

Fig. 2.—Smear of tissue fluid taken from apparently healthy tissue surrounding a noma lesion. There are numerous spirilla as well as fusiform and thick bacilli.

Fig. 3.—Liver, showing fat vacuoles and swelling of the stellate (Kupffer) cells with phagocytosis.

(fig. 5). The greater part of the dermal connective tissue was necrosed. All the vessels were thrombosed. Demarcation between thrombus and necrosed vessel wall was hardly recognizable. Only occasional nuclei in the debris took up the stain, and these were chiefly nuclei of nerve cells or of the precapillary vessels (fig. 6). The tissue had lost all regularity of shape, and even with hematoxylin stain extremely large numbers of bacteria and fungi were visible. Hemorrhagic spots were scattered over all the necrosed parts. In the deeper layers of the boundary zone, chiefly in the region of the striated muscles, there was some leukocytic infiltration with appreciable edema. This was chiefly visible in the region of demarcation between necrotic and living tissue (fig. 7).

The histologic examinations confirmed the impression that there must exist a toxic state which forces the noma virus to produce necro-

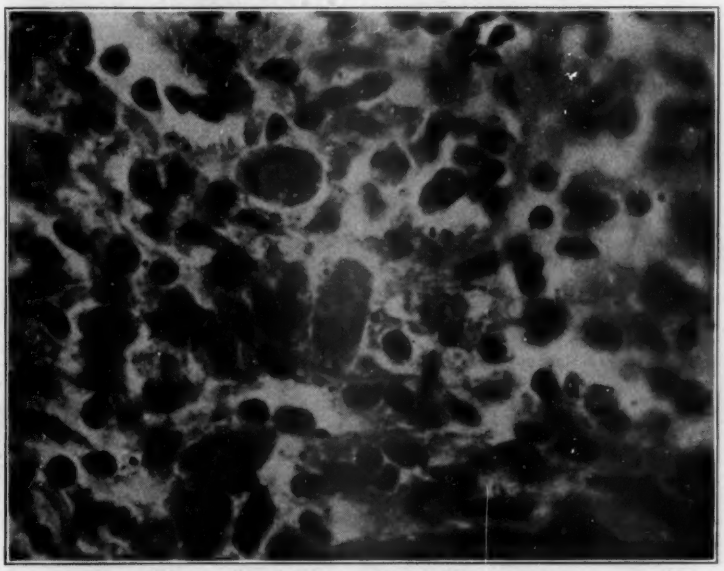

Fig. 4.—Spleen. Note swelling of the reticuloendothelium; × 845.

biosis. The bacterial emboli observed in remote organs can only be explained as secondary metastases from the primary focus. The histologic observations have been uniform both in my own studies and in those of Professor Oberndorfer.

As a result of my observations I shall now attempt to introduce some facts concerning the clinical aspects of noma. The question of the association of noma with stomatitis ulcerosa dates from the prebacterial era and is still considered in the modern literature. The finding of a common exciting cause in both conditions, i. e., the Plaut-Vincent symbiosis, supports this association. However, I doubt that the various forms of ulcerating stomatitis described in the prebacterial era were

really the entity recognized today by that designation. Mercurial stomatitis, seen not infrequently in those days, was also considered as giving rise to noma. Today there is lack of evidence to support any connection between mercurial stomatitis and real stomatitis ulcerosa, which Bohn [6] believed existed. Bohn followed many cases from their

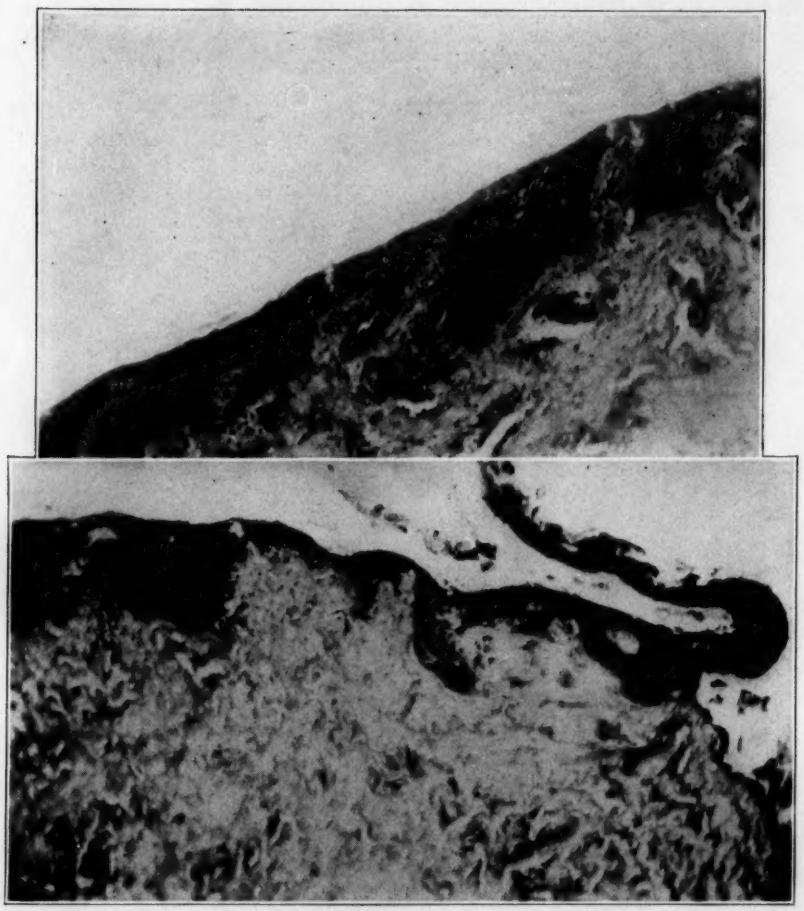

Fig. 5.—Section at the margin of a noma lesion, showing transition to the healthy tissue; × 75.

beginning and observed noma developing from ulcerous stomatitis. I am not now sure which kind of stomatitis Bohn meant. Fischl [7] also

6. Bohn, H.: Die Mundkrankheiten in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1880, vol. 4, pt. 2, pp. 3-128.

7. Fischl, in von Pfaundler, M., and Schlossmann, A.: The Diseases of Children, translated and edited by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935.

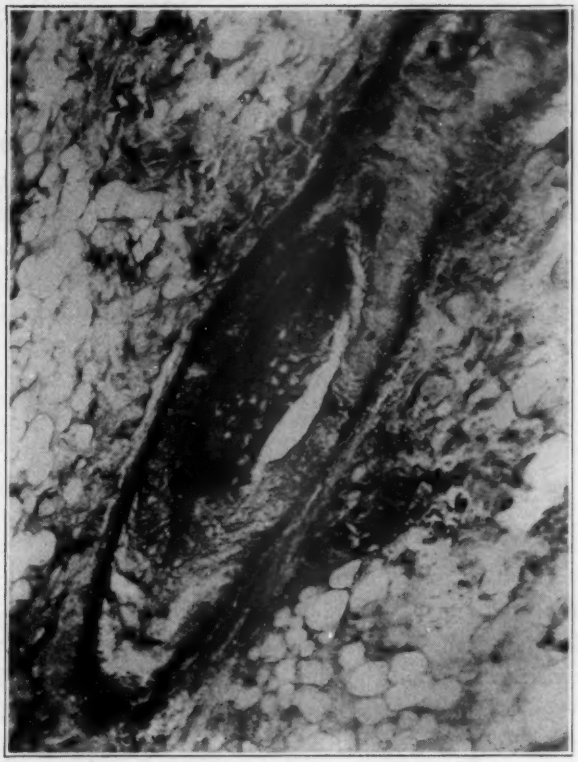

Fig. 6.—Noma, with section through a thrombosed necrotic artery; × 75.

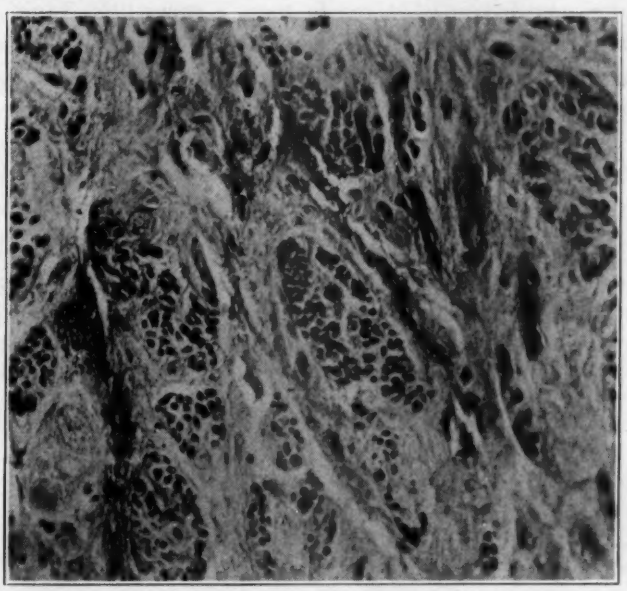

Fig. 7.—Noma, showing necrotic muscular tissue covered with bacterial flora. There is severe edema of the muscle; × 75.

noted his inability to find similar cases reported in modern literature. Perhaps the cause is that owing to better hygiene and nursing technic the epidemics of noma are no longer seen in hospitals, nurseries and other institutions as in the nineteenth century.

With the exception of 1 case we were never able to observe the actual onset of noma. In the other 39 cases the patients appeared at the hospital in more or less advanced stages of the disease. In this single case, however, the patient had typical ulcerous stomatitis at the time of entry. The smear showed the characteristic Plaut-Vincent symbiosis. In spite of active local treatment with neoarsphenamine applied as powder, typical noma developed in the cheek ten days after admission. This was the only patient of my series of 20 suffering with stomatitis ulcerosa and treated with neoarsphenamine powder who failed to recover. In this case not only were local applications of the powder maintained but 0.15 Gm. of neoarsphenamine was injected intravenously with no effect on the progress of the noma. This sole observation was sufficient to persuade me that noma may follow ulcerative stomatitis, although I am not able to maintain that this holds true in every case. Finally, I wish to mention the observations of Heinemann [8] and Sauerwald [9] on 47 cases collected in an epidemic of the Plaut-Vincent condition at Edirne (Adrianople), Turkey. In some of these cases noma developed and death ensued despite intensive treatment with neoarsphenamine.

Another peculiarity of noma is that it apparently leaves no local immunity after healing. There have been instances in which noma developed for the second time and gradually advanced on the site of an apparently healed lesion. Such recurrences may develop after weeks or months. An injury or traumatic irritation such as a plastic operation performed too early after the original healing may be factors giving rise to a recurrence.

These observations indicate that if any local immunity is developed it must be of short duration. Again it must be stressed that variations in general bodily resistance and immunity must play an important part in precipitating attacks of the disease. One of our patients had a relapse of noma following an attack of subtertian malaria. The noma responded readily to treatment with serum combined with a thorough course of atabrine.

Such instances remind one of the recrudescences which occur occasionally in pharyngeal diphtheria when some debilitating condition exists,

8. Heinemann: Berl. klin. Wchnschr. **54**:110, 1917.
9. Sauerwald: Berl. klin. Wchnschr. **54**:111, 1917.

chiefly in patients not treated with serum. Noma may well be compared with the toxic forms of diphtheria in the character of the progress of the disease. These two diseases may be compared in still another respect. The Plaut-Vincent symbiosis and the Klebs-Löffler bacillus usually give rise to ulcerative stomatitis and diphtheria, respectively, but under certain conditions each disease may develop a toxic form. Still further, with both diseases under certain as yet not well defined conditions carriers suddenly fall ill. This sequence may be the result of a fall in the resistance of the human organism.

Lastly, in comparing these two diseases I wish to consider the success or failure of the specific treatment. Uncomplicated pharyngeal diphtheria is just as surely influenced by prompt serum therapy as is ulcerative stomatitis by neoarsphenamine, and failure of the respective treatments is exceptional in either condition. But toxic diphtheria, despite large doses of specific serum, is often characterized by much less favorable results. Likewise noma, if defined as a toxic form of ulcerative stomatitis, can rarely if ever be cured with neoarsphenamine.

The fact that in toxic diphtheria the beneficial effect of the serum apparently has little to do with its specific action made us consider whether or not it might not be possible to find a suitable treatment for noma with a nonspecific serum. The parallelism of the results of nonspecific treatment in the two diseases, together with other points of similarity, increases the probability that noma is a toxic form of stomatitis ulcerosa.

To complete the comparison of these two diseases, I feel that just as some authorities consider that toxic diphtheria may be caused not by the Klebs-Löffler infection alone so in noma one should search for other causes than the Plaut-Vincent symbiosis. Just as the question may be posed as to why in one case Klebs-Löffler infection leads to simple diphtheria and in another to toxic diphtheria, so it may be asked why the Plaut-Vincent symbiosis leads in one case to ulcerative stomatitis and in another to noma. The problem appears clearer in the case of noma because there is little doubt that other noxae such as infectious diseases (malaria in my cases) may be held responsible as pacemakers. In regard to toxic diphtheria only a constitutional predisposition is at present accepted.

I wish now to describe our therapeutic measures in noma. First I should like to introduce the lethality records at my disposal. Most works on this subject refer to the records presented by Bruns (1859), which give 70 to 80 per cent as the death rate for noma. Bohn, how-

ever, expressed doubt as to the exactness of these figures and preferred to depend on the limited material he cited, as follows:

*Mortality in One Hundred and Seventy-Five Cases of Noma Cited in the Literature*

| No. of Cases | Author | No. of Fatalities |
|---|---|---|
| 10 | West | 8 |
| 21 | Rilliet and Barthez [10] | 20 |
| 108 | Steiner | 103 |
| 36 | Taupin | 36 |

Thus of a total of 175 cases cited 167, or 95 per cent, were fatal.

At the present time practically no clinicians have at their disposal a sufficiently large number of cases of noma to allow an exact expression of the case fatality. It can be said, however, that in any case the rate is elevated.

In treating our patients my associates and I were at first led to follow the advice of authorities to use neoarsphenamine. We were also inclined to adopt this method because of the favorable results it provides in the treatment of ulcerative stomatitis. In modern literature one finds a tendency to forsake this treatment (Fischl, Heinemann, Sauerwald) because it has proved ineffective. Unfortunately, I, too, have had to admit the failure of the neoarsphenamine treatment in noma. Of 9 patients treated with local applications of neoarsphenamine powder accompanied by the intravenous injection of 0.15 Gm. daily, 8 showed rapid progression of the necrotic process and a fatal termination. One patient admitted in an early stage with very limited necrosis showed amelioration after the second injection, and the lesion rapidly healed with sequestration of the necrosed tissue.

By some authors surgical intervention is also recommended. In 1 of our cases extirpation of the necrosed area including a considerable border of healthy tissue beyond the lesion proved unsuccessful. After a few days rapidly advancing necrosis of the surrounding tissues took place, and the course ended fatally.

After these therapeutic disappointments we tried antigangrene serum. I chose this serum at the time in hopes that it might have some specific action, but after our bacteriologic studies I began to believe that the beneficial effects of the serum lay really in a nonspecific action.

It is well established that tissue affected by noma is not sharply demarcated from the surrounding healthy tissue and that any inflammatory reaction in this zone is a good sign that there is an inclination to

10. Rilliet, F., and Barthez, E.: Traité clinique et pratique des maladies des enfants, ed. 3, Paris, Félix Alcan, 1887.

healing. This observation led us to inject the serum locally in the healthy tissue adjacent to the necrotic area. For this purpose we employed 10 cc. of serum. In addition to this local treatment we injected from 10 to 20 cc. of the serum intramuscularly and an equal amount intravenously. This treatment was repeated daily and was continued until sloughing of the necrosed tissues took place. By this time, on the average, about 500 cc. of serum had been administered.

Of 21 patients in more or less advanced stages of noma 11 progressed to complete recovery, and in these patients signs of demarcation were visible after the first local injection. In some of the remaining 10 cases signs of demarcation and temporary improvement were observed, but sooner or later the disease resumed its progression and

Fig. 8.—*A*, noma in a child aged 5 years. There is necrosis of the upper lip, and the lower lip and the lower part of the cheek are covered with crust. *B*, the same patient, showing healing after treatment with antigangrene serum.

the patients died. These cases differed from other fatal cases by a considerable prolongation of the course of the disease, which in some did not terminate until after more than four weeks of total duration. The comparatively favorable results of this treatment hold out, I believe, a favorable prognosis for the future.

It should be noted that in the comparison of the different methods of treatment 10 cases were dropped from consideration. In 7 of these the patients arrived at the hospital in a state of coma and died within twenty-four hours. Three other patients died on the second day after entry and were likewise considered to be already in a terminal stage of the disease.

In addition to the treatment with serum we also administered vigorous antimalaria treatment, using atabrine and plasmochin in all

cases in which plasmodia were demonstrable. Theoretically I do not consider that the antimalaria remedies have any direct influence on the noma virus. On the other hand they may have a positive effect by

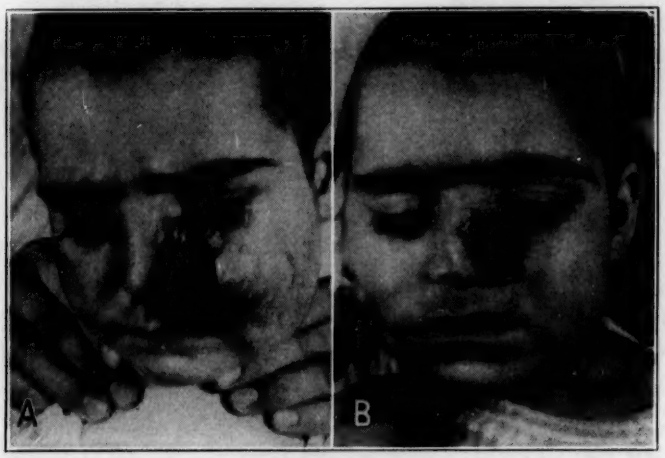


Fig. 9.—*A*, noma in a child aged 8 years, with necrosis of the left cheek. *B*, the same patient, showing healing after treatment with antigangrene serum. The defect leaves an opening into the maxillary sinus.

Fig. 10.—*A*, noma in a woman aged 20 years, with necrosis of the lower lip. *B*, the same patient, showing healing after treatment with antigangrene serum.

elevating the general resistance of the organism. Since malaria was so frequently observed in our cases I can logically indicate the treatment used as serum-atabrine-plasmochin therapy.

SUMMARY

During the years 1936 to 1938 inclusive 40 patients with noma were admitted to the service of the Children's Hospital, providing an opportunity to observe material hardly to be equaled in western Europe.

Seasonal distribution of the cases shows a marked prevalence in summer and autumn.

Sex distribution, contrary to classic descriptions, shows considerable predilection for the male sex.

In most of the cases the absence of vital reactions was striking: there was usually no fever, and there was practically no leukocytic reaction. During the early stage local necrobiosis was found, while in the late stage other symptoms of general intoxication or of secondary metastatic complications became prominent. As a predisposing factor malaria, chiefly of the subtertian type, played a predominant role. Only 2 patients suffered a preliminary attack of typhoid fever, while in only 1 case was measles (and malaria) a contributing factor. In only a few of the cases was there any tendency to cachexia or atrophy, which is contrary to claims of most other authors. Most of our patients showed a normal or strong degree of nourishment and health.

In a few of our cases relapses were noted some time after apparent recovery from the original attack.

The bacteriologic studies confirmed the classic findings of a mixed flora, and no agreement could be reached as to which organism was responsible. However, in each of the last 12 cases my associates and I were regularly able to demonstrate a pure culture of fusiform bacilli together with spirilla in the apparently healthy tissue just surrounding the noma. Consequently I agree with certain authors cited who consider that the Plaut-Vincent symbiosis is most likely the specific agent. I am also in a position to confirm the transition from stomatitis ulcerosa to noma, a condition claimed by older writers but never before subject to the control which it has been possible for us to make.

An attempt has been made to compare infection with the Klebs-Löffler bacillus with that of the Plaut-Vincent symbiosis in that carriers as well as a mild and a toxic form are to be observed with both diseases. It is thus suggested that noma can be regarded as a toxic form of stomatitis ulcerosa.

Study of the morbid anatomy in our cases showed signs of general intoxication which gave rise to changes in liver and spleen as well as to pulmonary emphysema. In some cases foci of necrotic pneumonia were noted. Histologic examinations showed necrosis and degenerative changes in spleen and liver. In the transition zone between healthy and necrotic areas of the lesions there were degeneration of the epidermal cells of varying degree, pigment deposits and hemorrhagic spots and

absence of vital reactions. In the deeper layers were to be seen thrombosis of the vessels with a destruction of the vessel walls as well as numerous bacteria and fungi.

Our attempts at therapy demonstrated the futility of depending on neoarsphenamine in noma. Eight of the 9 patients treated with local applications of the powder and intravenous injections died. Surgical treatment, attempted in 1 case, was also a failure.

Much more satisfactory results were obtained by the daily local use of antigangrene serum, injected into the neighboring tissue intramuscularly and intravenously. Large amounts of serum were used over comparatively long periods. I believe that the action of the serum is nonspecific. In cases of malaria we also administered atabrine and plasmochin. Eleven of the 21 patients treated in this manner recovered. This result encourages me to recommend this new method of treatment, in consideration of the grave prognosis which noma always presents.

NOTE.—Since the preparation of this paper (May 1939) I have been able to make certain further observations of interest.

A 3 year old girl appeared with an early lesion of noma on the upper lip which developed on scar tissue. This scar formed a wedge-shaped defect of the lip. There was accompanying gingivitis. We were able to establish that this child, who was even at the moment infected with malaria, had three months earlier suffered an attack of measles, at the conclusion of which noma had developed. The first lesion had healed spontaneously, leaving only the defect noted. Here again is a case of noma recurring on an original spontaneously healed lesion (case 42).

Later we encountered simultaneously 2 sisters (both infected with malaria) of whom 1, aged 1 year, had noma of the upper lip. The other sister, aged 3, had gingivitis with stomatitis of the upper lip. In both children smears taken from the lesions showed rich cultures of spirilla and fusiform rods. Of particular interest is the fact that the child now presenting herself with a typical noma had been in our clinic three months earlier, when, with neoarsphenamine, we had successfully treated her for ulcerative stomatitis. The relation between ulcerative stomatitis and noma seems here clearly established, and these cases further support my belief that noma is a toxic form of ulcerative stomatitis (case 43).

These recent observations have strengthened my view that there may be some causal agent playing a common role in noma and in the gingivitis which so often occurs simultaneously with noma. This combination of conditions is well demonstrated in the last case referred to in the present article (fig. 10). In this case, after the healing of the

noma lesion and of the accompanying gingivitis we wished to extract the teeth closest to the lesion, which were affected with encircling caries. The patient refused this precaution. Two months after recovery she returned with another well established attack of gingivitis at the site of the carious teeth and with recurrence of the noma on the site of the original scar. After extraction of the teeth and repetition of the treatment with antigangrene serum the lesions cleared rapidly. The view occasionally expressed in the literature that a relation exists between dental disease on the one hand and gingivitis with the rise of noma on the other seems, therefore, at least in a certain proportion of cases, reasonable indeed.

# THE DIABETIC CHILD

## AN ANALYTIC STUDY OF HIS DEVELOPMENT

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Many articles on the significant interrelation between physical and mental health have appeared in the literature during the past decade. Consideration of the health of the integrated diabetic child seems to be an important application of this concept, since in diabetes mellitus many phases of the metabolism are disturbed over a long period. In this disease, moreover, the physical aspects appear to be especially intimately interwoven with development of the child's mind and personality. For instance, the strict adherence to a rigid routine would be likely to make a child feel different from others and perhaps despondent.

It seems evident from the writings of Joslin,[1] who during the past thirty-five years has stimulated interest and spread knowledge concerning the study and care of diabetic patients,[1] that he considers and treats the whole diabetic person rather than merely the disease. He has expressed the desirability of gathering more complete data on diabetic children, although he has probably treated more young diabetic patients than any one else in this country. It appears, then, that the total number of cases considered is less important in an analysis of this sort than are the determination and selection of pertinent facts which are applicable to the members of the diabetic group. Murchison,[2] in the preface to the second edition of his "Handbook of Child Psychology," expressed regret that the role of nutrition and disease in the development of child behavior is "not yet sufficiently understood" to warrant the inclusion of a chapter on it in his book.

The purpose of the present investigation was to make a developmental analysis of a group of diabetic children that would be representative of the population of Minnesota. The physical and mental features

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From the Institute of Child Welfare and the Department of Pediatrics, University of Minnesota.

1. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935; ed. 6, ibid., 1937.

2. Murchison, C.: Handbook of Child Psychology, ed. 2, Worcester, Mass., Clark University Press, 1933.

and the personality of the diabetic child and of a sibling in normal health were observed and then compared in as many cases as possible. This paper will present a fairly full report of our findings in regard to some phases of the physical development of this group, both before and after the onset of diabetes, and will summarize the findings in the fields of intelligence and personality.[3] Although the objective genetic comparisons of this study are incomplete because of the paucity of measurements available for the period preceding the disease and for an identical time afterwards for diabetic children and their siblings, we feel that this study reveals some worth while findings and tendencies and may point the way to more complete investigations of this type.

TABLE 1.—*Age and Sex Distribution in Cases Used in This Study* *

| Age | Male | Female | Total |
|---|---|---|---|
| 1 yr., 6 mo. to 2 yr., 5 mo. | .. | 1 | 1 |
| 2 yr., 6 mo. to 3 yr., 5 mo. | .. | .. | .. |
| 3 yr., 6 mo. to 4 yr., 5 mo. | 1 | .. | 1 |
| 4 yr., 6 mo. to 5 yr., 5 mo. | .. | 1 | 1 |
| 5 yr., 6 mo. to 6 yr., 5 mo. | 2 | 1 | 3 |
| 6 yr., 6 mo. to 7 yr., 5 mo. | 2 | 1 | 3 |
| 7 yr., 6 mo. to 8 yr., 5 mo. | .. | .. | .. |
| 8 yr., 6 mo. to 9 yr., 5 mo. | 1 | 1 | 2 |
| 9 yr., 6 mo. to 10 yr., 5 mo. | 2 | 2 | 4 |
| 10 yr., 6 mo. to 11 yr., 5 mo. | .. | 4 | 4 |
| 11 yr., 6 mo. to 12 yr., 5 mo. | 2 | 6 | 8 |
| 12 yr., 6 mo. to 13 yr., 5 mo. | 3 | 2 | 5 |
| 13 yr., 6 mo. to 14 yr., 5 mo. | 2 | 2 | 4 |
| 14 yr., 6 mo. to 15 yr., 5 mo. | 3 | 6 | 9 |
| 15 yr., 6 mo. to 16 yr., 5 mo. | 3 | 5 | 8 |
| 16 yr., 6 mo. to 17 yr., 5 mo. | 2 | 2 | 4 |
| 17 yr., 6 mo. to 18 yr., 5 mo. | .. | .. | .. |
| 18 yr., 6 mo. to 19 yr., 5 mo. | .. | 2 | 2 |
| 19 yr., 6 mo. to 20 yr., 5 mo. | .. | .. | .. |
| 20 yr., 6 mo. to 21 yr., 5 mo. | .. | 1 | 1 |
| Total | 23 | 37 | 60 |

* Median age of group at time of study, 13 years and 1 month.

## SUBJECTS AND CONTROLS

The original diabetic group consisted of 60 subjects who ranged in age from 22 months to 20 years and 1 month but all of whom had the onset of diabetes before 15 years of age and all of whom regularly attend the Diabetic Clinic of the Pediatric Departments of the University of Minnesota Hospital or the Minneapolis General Hospital. Their age and sex distribution are shown in table. 1. Included in this group were all the diabetic children, without exception, who attended the University Hospital Clinic between Dec. 15, 1936, and May 1, 1937, numbering 42, and in addition 18 patients selected at random from the total of 25 regularly attending the General Hospital Clinic from April 16 to May 21, 1937. Limitations of time and of facilities prevented the inclusion of the remaining 7 at the Minneapolis General Hospital, but no apparent selective factor was present.

3. In *Child Development* for June 1938 is an article that treats more fully of the mental and personality development of this group of children (Brown, G. D.: The Development of Diabetic Children with Special Reference to Mental and Personality Comparisons, Child Development **9**:175, 1938.

The median age for the group at the onset of diabetes was 8 years and 3 months, and the mean duration of the disease up to the time of our study was 4 years and 9 months. The distribution of the patients according to age at onset is shown in table 2. One child's symptoms dated practically from birth.

Our diabetic group consisted of 37 girls (62 per cent) and 23 boys (38 per cent). This is surprising in view of Joslin's [1] saying that there was virtually no sex difference among his diabetic children, although he tabulated small but definite sex differences in favor of the boys in all age groups of childhood.[4] Joslin, Dublin and Marks,[4] John [5] and Adams [6] have found a large increase in the proportion of diabetic women between the ages of 45 and 65 since 1922, while Joslin [1] and Adams [7] reported that previous to that date there were greater numbers of male diabetic patients than female at nearly all ages. No definite recent sex trends are reported for diabetic children. Although our group is too small for us to draw any decided conclusions in this respect, the preponderance of girls from both urban and rural localities suggests that the greater frequency of diabetes among females may have its beginning during childhood. Joslin's much larger group certainly gives a more exact picture of the incidence during a long period, but no recent change can be detected from his data.

TABLE 2.—*Age at Onset of Diabetes in Cases Used in This Study* *

| Age at Onset | No. of Cases |
|---|---|
| Birth to 5 mo. | 1 |
| 6 mo. to 1 yr., 5 mo. | 1 |
| 1 yr., 6 mo. to 2 yr., 5 mo. | 1 |
| 2 yr., 6 mo. to 3 yr., 5 mo. | 3 |
| 3 yr., 6 mo. to 4 yr., 5 mo. | 6 |
| 4 yr., 6 mo. to 5 yr., 5 mo. | 7 |
| 5 yr., 6 mo. to 6 yr., 5 mo. | 6 |
| 6 yr., 6 mo. to 7 yr., 5 mo. | 1 |
| 7 yr., 6 mo. to 8 yr., 5 mo. | 6 |
| 8 yr., 6 mo. to 9 yr., 5 mo. | 3 |
| 9 yr., 6 mo. to 10 yr., 5 mo. | 7 |
| 10 yr., 6 mo. to 11 yr., 5 mo. | 7 |
| 11 yr., 6 mo. to 12 yr., 5 mo. | 4 |
| 12 yr., 6 mo. to 13 yr., 5 mo. | 5 |
| 13 yr., 6 mo. to 14 yr., 5 mo. | 0 |
| 14 yr., 6 mo. to 15 yr., 0 mo. | 2 |

* Median age at onset, 8 years and 2 months.

Table 3 shows that our cases had a wide variation in regard to duration of the disease at the time of this study.

Three of our patients have, or did have, a diabetic sibling, and in 1 instance all 3 children in the family were diabetic—a rare occurrence. Of these 4 diabetic siblings only 1 has died, death occurring in the year before insulin was discovered.

4. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: II. Its Incidence and Factors Underlying Its Variations, Am. J. M. Sc. **187**:433, 1934.

5. John, H. J.: The Growth of Diabetic Children, Am. J. Digest. Dis. & Nutrition **1**:855, 1935.

6. Adams, S. F.: An Inquiry into the Etiology of Diabetes: A Statistical Study, Thesis, University of Minnesota, 1927.

7. Adams, S. F.: The Seasonal Variation in the Onset of Acute Diabetes: The Age and Sex Factors in One Thousand Diabetic Patients, Arch. Int. Med. **37**:861 (June) 1926.

Our children included a pair of dissimilar twins, only one of whom had diabetes. Joslin[1] reported that in 9 of his 13 sets of similar twins both were diabetic, whereas in only 2 of his 16 pairs of dissimilar twins did both have the disease. This 12 per cent incidence is, however, three times that of the incidence among diabetic siblings generally. In our small series (table 6), the percentage of incidence among siblings is greater than that in Joslin's series.[1]

It was considered important that our subjects and controls should constitute as nearly as possible a representative sampling of the population from which they were drawn. This is especially true since we are dealing with an uncommon condition. The Goodenough-Anderson[8] occupational classification as applied by Baker[9] to the Minnesota population was used in determining the socioeconomic status of our subjects. As the data presented in table 4 indicate, our clinic children constitute a group representative of the state population, especially if we combine the closely related groups 1 and 2 and also combine the poorly differentiated groups 6 and 7 of this socioeconomic scale.

TABLE 3.—*Duration of Diabetes in Cases Used in This Study* *

| | No. of Cases |
|---|---|
| 0 yr. to 12 mo. | 6 |
| 1 yr. to 1 yr., 11 mo. | 7 |
| 2 yr. to 2 yr., 11 mo. | 8 |
| 3 yr. to 3 yr., 11 mo. | 8 |
| 4 yr. to 4 yr., 11 mo. | 5 |
| 5 yr. to 5 yr., 11 mo. | 5 |
| 6 yr. to 6 yr., 11 mo. | 7 |
| 7 yr. to 7 yr., 11 mo. | 5 |
| 8 yr. to 8 yr., 11 mo. | 1 |
| 9 yr. to 9 yr., 11 mo. | 4 |
| 10 yr. to 10 yr., 11 mo. | 2 |
| 11 yr. to 11 yr., 11 mo. | 1 |
| 12 yr. to 12 yr., 11 mo. | 1 |

* Mean duration, 4 years and 9 months; median duration, 4 years and 2 months.

The revised diabetic group referred to in table 4 consisted of 54 patients in our original group who had no complication which might have interfered with normal development, plus 3 especially selected diabetic patients who were without complications (1 of whom was a private patient and 1 a college student). The inclusion of these 3 subjects brought the socioeconomic distribution of our diabetic group into still closer conformity with that of the general Minnesota population. Both groups are, however, not sufficiently representative of the farming population of the state (group 4 is composed entirely of farmers) unless, as Joslin, Dublin and Marks[4] suggested, diabetes is more prevalent in the city population.

It may seem surprising that clinic patients represent the general population so well as our group does. Our hospital clinics, it should be said, admit diabetic children more liberally than children with other diseases. The diabetic children are received from all parts of Minnesota according to their parents' present economic need and irrespective of their parents' occupational status because the hospitals recognize the lifelong duration of the disease and the expense involved for insulin and specific diets. Over half of the University Hospital group pay for

8. Goodenough, F. L., and Anderson, J. E.: Experimental Child Study, New York, D. Appleton-Century Company, Inc., 1934.

9. Baker, K. H.: Radio Listening and Socio-Economic Status, Psychol. Rec. 1:99, 1927.

their visits, and about one third of the General Hospital group pay varying small amounts.

The socioeconomic status of Joslin's groups of children,[10] on which he based his conclusions as to their precocity in height and intelligence, was not mentioned specifically, although all socioeconomic groups were said to be represented.[11] It seems unlikely, however, that the total of 1,126 diabetic children treated by him since 1898 or the 463 seen from 1929 to 1934 represented the general population of any geographic area. Joslin is so eminent a specialist that his patients come from all sections of the country, only two thirds of them residing in his own densely populated state.[12] It seems improbable that many patients in the lower socioeconomic groups could afford the time and money necessary to take children from distant localities to the George F. Baker Clinic in Boston. Whatever may be construed from the term "middle class" or "average," it should be realized that the general population is not divided equally in number into "upper," "middle" and "lower" classes (see Baker,[9] Goodenough and Anderson[8] and table 4). It has been reported[12a] that 21.8 per cent of Joslin's entire group of patients are "engaged in professional and semiprofessional pursuits," the proportion of physicians and surgeons alone being 6.9 per cent. There is, however, a possibility that the incidence of diabetes is associated to a slight extent with occupational status, as Joslin, Dublin and Marks[13] suggested, the incidence being greater among the more leisured, wealthy and gourmand.

TABLE 4.—*Distribution of Diabetic Children According to Socioeconomic Status of Their Parents*

| Socioeconomic Group | Minnesota Population, % | | Original Diabetic Group* No. | Original Diabetic Group* % | | Revised Diabetic Group,* % | |
|---|---|---|---|---|---|---|---|
| 1. Professional | 2.33 | | 1 | 1.7 | | 3.51 | |
| 2. Business executives | 7.26 | 9.64 | 5 | 8.3 | 10.0 | 7.02 | 10.53 |
| 3. Retailers; skilled workers | 12.77 | | 9 | 15.0 | | 15.79 | |
| 4. Farmers | 22.61 | | 12 | 20.0 | | 17.54 | |
| 5. Semiskilled workers | 21.37 | | 14 | 23.3 | | 24.56 | |
| 6. Slightly skilled workers | 9.05 | | 9 | 15.0 | | 15.79 | |
| 7. Laborers | 24.56 | 33.61 | 10 | 16.7 | 21.7 | 15.79 | 33.61 |

* Total in original group, 60; in revised group, 57.

Of the 45 subjects of our group for whom we had definite information concerning nationality, 10 were "old Americans" of at least three generations. The parents of 19 were Scandinavian, of 10 Germanic or semi-Germanic, of 5 predominantly Anglo-Saxon, and of 8 Slavic or semi-Slavic. Only 4 were Jewish or part Jewish. This nationality distribution is typical of the Minnesota population.

10. (*a*) White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932. (*b*) Joslin and others.[1]

11. White, P.: Personal communication to the author, Boston, 1937.

12. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: (*a*) Studies in Diabetes Mellitus: IV. Etiology, Part I, Am. J. M. Sc. **191**:759, 1936; (*b*) footnote 4.

13. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: I. Trends of Diabetes Mortality Throughout the World, Am. J. M. Sc. **186**:753, 1933; III. Interpretation of the Variations in Diabetes Incidence, ibid. **189**:163, 1935.

All our patients proved to have diabetes mellitus by a value for venous blood sugar during fasting of over 140 mg. per hundred cubic centimeters or a peak in the dextrose tolerance curve of over 200 mg. with the blood sugar value after two and one-half hours above 140 mg. and associated with persistent glycosuria. Believing that the best single measure of the severity of diabetes is the amount of insulin per unit of body weight required to keep the patient almost free of glycosuria, we have recorded this in table 5. Our subjects range from one who takes no insulin to one who takes over 1 unit per pound (0.45 Kg.).

Our controls were healthy siblings of the diabetic children. It was felt that controls of this type would provide a more exact comparison than children selected at random from the Minnesota population. At the same time it was realized that the sibling of a diabetic child has a much greater likelihood of becoming diabetic himself than the average child has.[1] We attempted to diminish this possible error by choosing, whenever possible, the next older rather than the next younger child. We were able to use such sibling controls for objective comparison in 28 cases and, in addition, to use siblings for subjective comparison in a total of 48 cases. The median age of the controls was 14 years and 6 months and their mean age 13 years and 10 months.

TABLE 5.—*Units of Insulin per Pound of Body Weight Required by the Original Sixty Patients*

| Units of Insulin | No. of Cases |
|---|---|
| 0—0.1 | 1 |
| 0.11—0.2 | 3 |
| 0.21—0.3 | 6 |
| 0.31—0.4 | 15 |
| 0.41—0.5 | 12 |
| 0.51—0.6 | 10 |
| 0.61—0.7 | 10 |
| 0.71—0.8 | 1 |
| 0.81—0.9 | 1 |
| Over 0.91 | 1 |

## PROCEDURE

Records were analyzed for all the diabetic children registered at the University Hospital and at the General Hospital. From these records were obtained the date and type of onset of diabetes, the family and the developmental history and clinical and laboratory findings, including height and weight. Each patient and control studied was given a physical examination. At least one urinalysis was made for all controls. Both the patient and his parents were questioned in detail, verbally and by questionnaire, regarding the onset of diabetes, and the parents were interrogated as to the incidence of diabetes and other diseases in the family, as to their nationality and occupation and as to a general and specific comparison of the personality of the diabetic child with that of his sibling. All the diabetic subjects and siblings included in this study were tested by the revised Stanford-Binet individual scale for measuring intelligence. Most of the tests were administered and the remainder were supervised by Miss Barbara A. Mayer, psychometrist at the Institute of Child Welfare. All tests were given in a quiet room, with no one present except the child and the examiner. The Advanced Otis Group Intelligence Tests and the Woodworth-Cady Psychoneurotic Inventory were also applied to all children with a mental age of 9 years or over. Data on the children's progress, attendance and behavior were obtained from the schools they attended. All parents and children cooperated readily in the study. Fifty-four questionnaires

for parents, or 90 per cent of the total, were returned completely or almost completely answered. School reports were returned for 35 diabetic children and 16 siblings.

## OBSERVATIONS

*Physical Rating.*—One of the main points reported on in the questionnaire for parents and confirmed by oral questioning was the incidence of diabetes among relatives of the diabetic child. Table 6 gives these data. This family incidence is approximately that reported by Joslin.[1] It is interesting that in spite of the high family incidence in our group, only 1 parent of a diabetic child had the disease, particularly since heredity and overweight appear to be the two chief predisposing factors in adults [13a] (as we shall show later, one fourth of the parents of our

TABLE 6.—*Incidence of Diabetes and Other Endocrine Disturbances in Families of Diabetic Subjects*

| Relative | No. of Cases of Diabetes | No. of Cases of Other Endocrine Disturbances |
|---|---|---|
| Sibling | 10 | 5 |
| Parent | 1 | 5 |
| Parent's sibling | 18 | 10 |
| Grandparent | 6 | 3 |
| Grandparent's sibling | 11 | 1 |
| Other relative (greatgrandparent, cousin, etc.) | 21 | 1 |
| Total cases in families | 67 | 20 |
| Diabetic subjects reporting any other instance of diabetes in family (56.7 per cent of total group) | | 34 |
| Diabetic subjects with diabetic siblings or parent (10.0 per cent of total group) | | 6 |
| Mean number of diabetic relatives of subjects who reported any instance of diabetes in the family | | 2 |

diabetic children were overweight). The only other physical abnormality which was reported in the families of our diabetic subjects to a greater extent than in the general population is a disturbance in the functioning of the thyroid gland. This condition was known to be present in 4 siblings, 4 parents and 10 parents' siblings.

So far as could be determined, only 10 of our diabetic children have, or ever have had, complications or other diseases of more than three months' duration. Three of our subjects had ocular involvement. The condition of 1 child, whose diabetes was poorly controlled, was diagnosed as retrobulbar optic neuritis with central scotomas and almost complete blindness. Within three months of the establishment of a good diabetic regimen, vision was restored and all signs of the neuritis and scotomas disappeared. Another child, who had had diabetes for twelve years and who had been on a liquid diet without insulin for several years

13a. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: V. Heredity, Am. J. M. Sc. **193**:8, 1937.

after the onset, had on admission to the hospital central retinitis (also reported in 3 of Joslin's cases [1]). Only 1 of our children had cataracts, and she has been a chronic breaker of the diabetic regimen for the ten years during which she has had the disease. Seven of Joslin's children with cataracts had experienced the onset of diabetes before the discovery of insulin. In only 1 of the patients with cataracts was diabetes under control at the time of the examination, and even his condition had been uncontrolled for "a long period."

Basal metabolic rates were determined only for children who had suggestive or pathognomonic signs of hypothyroidism or hyperthyroidism. The 2 most interesting and unusual patients in our group were those who had hypothyroidism, as evidenced by clinical signs and basal metabolic rates below — 15 per cent.

It is astonishing that in our small group of children there should be 2 having hypothyroidism, even more so when it is considered that these 2 were among the group of 42 from the University Hospital. The rather favorable effect of the hypothyroid state on diabetes has been known for some time. Lusk [14] stated that myxedema might abolish diabetes, which might, however, return with a return to a normal basal metabolic level. Greenwald and Collens [15] reported: "In a careful search of the literature we could find only 5 cases of diabetes associated with hypothyroidism," and added a case of their own. Joslin and White [1] reported only 1 case of these disorders in association.

(We studied with special interest a little boy, under 2 years of age when first seen at the clinic, who had marked hypothyroidism, being in fact a borderline cretin; but although he had glycosuria he had only a high normal blood sugar level during fasting [120 to 140 mg.]. The blood sugar has since reached a level definitely within normal limits, so that the child is only potentially diabetic now. His intelligence quotient, reported at about 1 year of age as between 70 and 80, has risen to over 100.)

One of our hypothyroid children also has epilepsy, which was not definitely diagnosed before the onset of diabetes, but she had a history of seizures, dating back to babyhood, that were definitely epileptic rather than hypoglycemic. At the time of writing she has about one epileptic convulsion a month. On several such occasions determinations of blood sugar have been average or high. This epileptic condition enhances the difficulty of keeping her diabetes controlled. Joslin and White [1] reported 7 cases of epilepsy among their patients, in 5 of which diabetes antedated the onset of epilepsy.

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14. Lusk, G.: Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

15. Greenwald, H. M., and Collens, W. S.: Hypothyroidism Complicated by Diabetes Mellitus, Am. J. Dis. Child. **50**:979 (Oct.) 1935.

A hand of a boy in our group had become gangrenous before he was seen at the clinic and brought under control. Since that time, six years ago, he has had no complications. White [10a] reported no gangrene among the diabetic children at the New England Deaconess Hospital.

Chronic otitis media and mastoiditis developed in 2 of our cases. One child in the group has asthma and 1 chronic sinusitis. Appendectomies were performed on 2 of our diabetic patients, in 1 case six months before the onset of diabetes and in 1 case after the onset.

The great majority of our patients had a gradual onset of diabetes. Polyuria, polydypsia and usually polyphagia (later associated with loss of weight and lessened activity) were present for some months in most of the patients prior to the diagnosis of diabetes or to the development of acidosis or coma. The exact interval is difficult to establish in retrospect. In 7 cases the period of onset, which was apparently shorter than two weeks but longer than one week, may be characterized as "rapid." In 1

TABLE 7.—*Parents' Estimate of General Health of Diabetic Children as Compared with Siblings*

| Time | No. in Better Health | No. in Equally Good Health | No. in Worse Health | Total No. of Children |
|---|---|---|---|---|
| Before onset | 11 | 29 | 7 | 47 |
| During previous year | 11 | 23 | 2 | 36 |

of our patients (whose sister already had the disease) symptoms developed "suddenly," within twenty-four hours after a tonsillectomy. Just before this operation her urine was reported normal. (For comparison, see Joslin.[1])

As table 7 shows, parents' reports indicated that a few more of the present diabetic children enjoyed better health than their sibling controls before the onset of their disease, while only 2 were considered to have been in poorer health than their siblings during the preceding year.

As to common colds, parents reported for 40 diabetic and control subjects that 17 diabetic patients had had more colds than their siblings during the past year, that 8 had had the same number and that 14 had had fewer. This seems to indicate that diabetic persons may be kept as free from colds as nondiabetic.

Nine of our diabetic subjects, or 15 per cent, were reported as having had pneumonia before they had diabetes. Although this is definitely above Joslin's [1] figure of 10 per cent, none of our patients had had pneumonia within a year of the onset of diabetes, which seems to exclude this disease as a cause. Eighteen children (one third of those for whom we have data) reported some acute infection other than colds within the

six months preceding the onset of diabetes, whereas White and Joslin [10] reported only a 10 per cent incidence of acute infection for the year prior to onset. The infectious diseases that our diabetic children had just before onset were both virus and streptococcic in etiology. The most prevalent were measles, tonsillitis and scarlet fever.

Over half our patients have had ketosis or acidosis and over one-third have been in coma or semicoma at least once; while only 4 have had more than three attacks of ketosis or acidosis, these children have experienced these states from six to fifteen times. About two thirds of the group reported having had at least one insulin shock, and 7 have had more than five. These data, however, are not reliable. Factors that tend to make them of little value for future application are the differences in the duration of the disease and the type and course of onset, early treatment or lack of it, questionable reliability of the parents' reports and variation in adherence by the patients to the prescribed regimen.

TABLE 8.—*Birth Weights of Diabetic Subjects and Their Siblings**

| | Below 5 | 5 to 5.9 | 6 to 6.9 | 7 to 7.9 | 8 to 8.9 | 9 to 9.9 | 10 to 10.9 | 11 to 11.9 | 12 or over | Total No. |
|---|---|---|---|---|---|---|---|---|---|---|
| Diabetic subjects... | 1 | 2 | 13 | 13 | 10 | 5 | 3 | 2 | 0 | 49 |
| Siblings..... | 1 | 1 | 6 | 11 | 9 | 5 | 3 | 0 | 1 | 37 |

* Values indicate pounds.

Heights and weights for both the children and their parents were recorded in as many cases as possible. The height and weight of the parents, as reported by 45 of them on the questionnaires, were found to be definitely abnormal for over one fourth. If one regards as abnormal a 10 per cent deviation in the same direction occurring in both parents and a 20 per cent deviation occurring in only one, then 12 pairs of parents were overweight and 2 pairs were underweight. Two pairs of parents and 2 single parents were much shorter than the average, and 2 single parents were significantly taller than the average.

The birth weights of the diabetic children fall into an essentially normal distribution, almost three fourths being between 6 and 8.9 pounds (2,722 and 4,037 Gm.). It will be seen in table 8 that a slightly greater percentage of nondiabetic than of diabetic subjects were below 7 pounds (3,175 Gm.) at birth.

Deviations from normal weight at the time of the study were no greater for the diabetic patients than for their siblings. Table 9 shows that the greatest frequency falls in the middle group. Only shortly after the onset of diabetes and before control was established, or for a short time thereafter, were the weights of the majority of the children more than 10 pounds (4,536 Gm.) below the averages we employed. This

table does not reveal the true picture of their weight in relation to the period after control was established, as many of the patients were not seen in our clinic for a year or more after the onset of diabetes.

It will be noted that the deviations in weight and height have been expressed by tabulating the number of children above or below the average in several periods related to the onset of diabetes. This was done so that comparisons with other studies, especially Joslin's, might be facilitated. (We realize, however, that both weight and height are better expressed in percentile ranks.[16]) Although Sherrill [17] tabulated deviations in weight for some of his diabetic children and also presented

TABLE 9.—*Number of Diabetic Children Deviating from Normal Weight at Various Periods Before and After Onset* *

| Deviation from Average Weight, Lb. | 12 to 24 Mo. Before | 6 to 12 Mo. Before | Onset to 6 Mo. After | 6 to 12 Mo. After | 12 to 24 Mo. After |
|---|---|---|---|---|---|
| 21 or more below | | | | | |
| Wood † | 1 | 1 | 7 | 4 | 8 |
| Minneapolis ‡ | 1 | 1 | 7 | 4 | 8 |
| 11 to 20 below | | | | | |
| Wood | 2 | 2 | 6 | 1 | 16 |
| Minneapolis | 5 | 1 | 4 | 6 | 12 |
| 6 to 10 below | | | | | |
| Wood | 2 | 1 | 6 | 11 | 0 |
| Minneapolis | 2 | 0 | 4 | 3 | 0 |
| 5 below to 4 above | | | | | |
| Wood | 7 | 3 | 8 | 5 | 26 |
| Minneapolis | 4 | 3 | 7 | 4 | 21 |
| 5 to 14 above | | | | | |
| Wood | 5 | 0 | 2 | 0 | 9 |
| Minneapolis | 3 | 0 | 0 | 0 | 9 |
| 15 to 24 above | | | | | |
| Wood | 0 | 0 | 0 | 0 | 2 |
| Minneapolis | 0 | 0 | 0 | 0 | 2 |
| 25 or more above | | | | | |
| Wood | 0 | 0 | 0 | 0 | 1 |
| Minneapolis | 1 | 1 | 0 | 0 | 1 |

* The number of cases in each interval varies because of availability.
† "Wood" indicates Baldwin-Wood revised 1923 tables.
‡ "Minneapolis" indicates Minneapolis school averages.[10a]

changes in height occurring at varying periods after the onset of diabetes, he did not tabulate or discuss deviations from normal height. No tabulations of deviations in either height or weight were found for any of Joslin's groups. Joslin [1] reported that "overheight amounting to an average of 2.4 inches occurred in 87 per cent of 303 diabetic children measured within three months of onset of symptoms." White [10a] expressed the belief that this increased height at the onset of the disease

16. (*a*) Burgess, M. A.: The Construction of Two Height Charts, J. Am. Statist. A. **32**:290, 1937. (*b*) Gray, H., and Ayres, J. G.: Growth in Private School Children, Chicago, University of Chicago Press, 1931.

17. Sherrill, J. W.: Juvenile Diabetes: Growth and Stature Changes, California & West. Med. **28**:788, 1928.

is responsible for a slight diminution in the rate of growth of diabetic children. Boyd [18] recently contended that his diabetic children were not above average height at the onset of the disease and that they showed no consistent trend in height at any time before or after the onset.

According to average heights for Minneapolis children (table 12), more of our diabetic group are below average than above at every period, but according to the Burgess records (table 12) there is no period in which a significant deviation occurs (table 10). The Minneapolis aver-

TABLE 10.—*Number of Diabetic Children Deviating from Average Height for Their Age at Various Periods Before and After Onset*

| Deviation from Average Height, In. | 6 to 36 Mo. Before | 6 Mo. Before to Onset | Onset to 6 Mo. After | 6 to 24 Mo. After | Present Time |
|---|---|---|---|---|---|
| **Above Average** | | | | | |
| 7 to 10* | | | | | |
| Burgess † | 1 | 0 | 0 | 0 | 0 |
| Minneapolis ‡ | 0 | 0 | 0 | 0 | 0 |
| 5 to 6 | | | | | |
| Burgess | 1 | 0 | 1 | 0 | 1 |
| Minneapolis | 1 | 0 | 0 | 0 | 0 |
| 3 to 4 | | | | | |
| Burgess | 3 | 3 | 0 | 2 | 6 |
| Minneapolis | 1 | 0 | 0 | 2 | 1 |
| 1 to 2 | | | | | |
| Burgess | 4 | 5 | 3 | 6 | 7 |
| Minneapolis | 3 | 2 | 2 | 5 | 6 |
| **Average** | | | | | |
| Burgess | 5 | 0 | 8 | 4 | 9 |
| Minneapolis | 0 | 3 | 0 | 3 | 3 |
| **Below Average** | | | | | |
| 1 to 2 | | | | | |
| Burgess | 5 | 2 | 4 | 7 | 8 |
| Minneapolis | 7 | 3 | 7 | 6 | 9 |
| 3 to 4 | | | | | |
| Burgess | 0 | 0 | 1 | 5 | 6 |
| Minneapolis | 6 | 2 | 5 | 6 | 6 |
| 5 to 6 | | | | | |
| Burgess | 0 | 0 | 0 | 0 | 1 |
| Minneapolis | 1 | 0 | 2 | 2 | 2 |
| 7 to 10 | | | | | |
| Burgess | 0 | 0 | 0 | 0 | 1 |
| Minneapolis | 0 | 0 | 0 | 1 | 3 |

* These measurements are all inclusive.
† "Burgess" indicates Burgess records.
‡ "Minneapolis" indicates Minneapolis school averages.

ages seem to constitute the most reliable standard available for our purpose, since they are based on recent measurements of local children from both upper and lower economic levels.

It is regrettable that we have practically no measurements of height for our patients as infants and few made prior to the onset of diabetes. It is fairly reasonable to assume that, as the marked disturbance in

18. Boyd, J. D.: Diseases of the Pancreas—Diabetes, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 12.

metabolism occurring during the early stage of the disease results in considerable loss of weight and strength, there would be a concomitant diminution, if not a temporary cessation, of growth in height. If this is so, then measurements taken three months or more after the onset of diabetes would fail to show the true deviation in height as it was just at the onset in these cases, and an increase in height above the average after establishment of control would appear less marked as compared with the increments of normal children than it really is. Table 11 compares the heights of 16 of our diabetic subjects with those of their siblings at various periods.

### INTERPRETATIONS

One factor that may account for the difference in rate of growth after control is established between our diabetic group and Joslin's group is a difference in diet. Our children, like those reported by Boyd and Nelson,[19] were kept on a diet "calculated to provide for full activity,"

TABLE 11.—*Comparison of Heights of Sixteen Diabetic Subjects and Their Siblings at the Same Chronologic Age at Various Periods Before and After Onset*

| Period | Diabetic Child 1 in. or More Taller | Diabetic Child and Sibling Approximately Same | Sibling 1 in. or More Taller |
|---|---|---|---|
| Over 2 yr. before onset | 4 | 2 | 4 |
| 2 yr. or less before onset | 5 | 4 | 2 |
| Onset to 2 years after onset | 2 | 2 | 1 |
| Over 2 yr. after onset | 4 | 1 | 4 |

while Joslin's (according to Boyd and Nelson) received from a half to three quarters of that amount. This fact, together with the probability that his children have the type of height curve shown by the "better class" of Minneapolis school children,[20] may partially explain why, Joslin's children were taller at the onset of diabetes and afterward tended to show less than the average annual growth rate established by national norms (Joslin;[1] Joslin, Dublin and Marks[21]). If a diabetic subject is much taller than a matched control, it may well be that this overgrowth resulted from a common metabolic change, probably pituitary in origin. Two of our patients did have an enormous spurt in growth during the year preceding the onset of diabetes. From our small group

19. Boyd, J. D., and Nelson, M. V.: Growth Studies of Children with Diabetes Mellitus, Am. J. Dis. Child. **35**:753 (May) 1928.

20. Weisman, S. A.: Contour of the Chest in Children: III. Environment, Am. J. Dis. Child. **49**:52 (Jan.) 1935.

21. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: IV. Etiology, Part II, Am. J. M. Sc. **192**:9, 1936.

of cases in which heights prior to the onset of the disease were known, and from Boyd's few cases it appears probable that the causes of diabetes may not be so uniform as are the symptoms of diabetes at onset. A derangement of the pancreas or of the pituitary gland may be the precipitating agent in some cases, infection in others and some yet unknown factor in the majority. We are inclined to agree with Joslin, Dublin and Marks,[21a] John [22] and others, however, that heredity is usually, if not always, the most powerful predisposing factor.

Both the small number of measurements available for comparisons of heights in this study and the confusion that exists in the matter of so-called standards for children's heights preclude the drawing of any definite conclusions on the relative heights of diabetic children. It will be seen from table 10 that, of the small number of diabetic children for whom we have data on height prior to the onset of the disease, according to the Burgess norms more were above than were below the average for their age, while according to the Minneapolis standards about twice as many were below average height as were above. We are glad that this apparent discrepancy results from applying these two standards to our height data, for it may serve to enforce the point that height and weight averages are not stationary. As table 12 shows, there are decided differences among the composite norms compiled by Burgess,[16a] the average heights of Minneapolis school children compiled by Weisman [20] and the average heights for private school children compiled by Richey.[23] All these norms are the results of recent and reliable studies.

It seems evident that drawing conclusions about present or recent heights from a restricted population by comparison with the old national norms is open to several serious errors. In the first place, present day children have been shown by an analysis made at Harvard University [24] by the Pearson study of English children [25] and by other studies to be taller than those of the preceding generation, on whom the older standards, including the Burgess composite, are based. Second, the several nationality groups show considerable variations in height,[26] and, third,

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21a. Joslin and others (footnotes 13 and 13a).

22. John, H. J.: The Diabetic Child: Etiologic Factors, Ann. Int. Med. **8**:198, 1934.

23. Richey, H. G.: The Relation of Accelerated, Normal, and Retarded Puberty to the Height and Weight of School Children, Monograph of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 1 (serial no. 8).

24. Bowles, G. T: New Types of Old Americans, at Harvard and at Eastern Women's Colleges, Cambridge Mass., Harvard University Press, 1932.

25. Hogben, L.: Genetic Principles in Medicine and Social Science, London, Williams & Norgate, 1931.

26. (*a*) Freeman, F. S.: Individual Differences, New York, Henry Holt & Company, Inc., 1934. (*b*) Bowles.[24] (*c*) Gray and Ayres.[16b] (*d*) Richey.[23]

definite deviations occur within the same national and racial groups, depending on socioeconomic status as well as heredity.[27] Certainly two of these factors, i. e., the use of old standards and the relatively high socioeconomic status of Joslin's group, and probably all three, tend to augment any real increase in height present in his children at the onset of the disease. Joslin, Dublin and Marks [12a] mentioned a preponderance of Jews among his patients as well as a high percentage of old Americans (compare with Freeman [26a] and Hogben [25]).

It would be advantageous if there were height and weight ranges for children in various localities.[28] These could be revised every decade or two, if a sampling suggested the necessity. These would be of most importance when a relatively small group of special subjects, such as those in this study, are being compared with the normal general population.

TABLE 12.—*Comparison of Three Height Norms for Boys and Girls Aged Five to Fourteen Years*

| | Height for Boys, In. | | | | Height for Girls, In. | | | |
|---|---|---|---|---|---|---|---|---|
| | | Minneapolis | | | | Minneapolis | | |
| Age, Yr. | Burgess Composite | Upper Class | Lower Class | Richey Private School | Burgess Composite | Upper Class | Lower Class | Richey Private School |
| 5 | 42.79 | 45.6 | 44.3 | ..... | 42.44 | 47.0 | 44.8 | ..... |
| 6 | 45.03 | 47.7 | 45.8 | 46.62 | 44.68 | 47.0 | 46.4 | 45.98* |
| 7 | 47.13 | 49.0 | 48.3 | 48.84 | 46.78 | 50.0 | 48.1 | 48.02 |
| 8 | 49.13 | 52.0 | 50.9 | 50.86 | 48.78 | 52.0 | 48.6 | 50.39 |
| 9 | 51.05 | 53.8 | 52.5 | 52.91 | 50.70 | 54.0 | 52.4 | 52.43 |
| 10 | 52.91 | 56.0 | 54.3 | 55.11 | 52.64 | 57.0 | 54.4 | 54.88 |
| 11 | 54.71 | 58.0 | 57.7 | 57.10 | 54.76 | 58.0 | 57.2 | 57.14 |
| 12 | 56.45 | 59.5 | 58.2 | 59.02 | 57.11 | 59.9 | 59.2 | 59.79 |
| 13 | 58.61 | 62.0 | 60.9 | 61.32 | 59.45 | 61.0* | 61.8 | 61.82 |
| 14 | 61.05 | 63.0* | 62.8 | 63.66 | 61.11 | 61.0* | 62.7 | 63.14 |

* Based on a small number of cases.

*Intelligence Rating.*[29]—Joslin's and White's assertion that the diabetic child is mentally precocious was probably at first a clinical impression (held also by other physicians such as Drs. F. S. Smyth and H. F. West of California [17]) which was later verified by mental tests given individually. No mention is made of the basis on which this relatively small group was selected from their total large group of children or of the representative character of either one, except in general terms in a personal communication.[11] Furthermore, medical and psychologic litera-

27. Growth and Development of the Child: III. Nutrition, White House Conference on Child Health and Protection, New York, Century Company, 1932. Gray and Ayres.[16b] Hogben.[25] Richey.[23] Weisman.[20]

28. Faber, H. K.: A Weight Range Table for Children from Five to Fifteen Years of Age, Am. J. Dis. Child. 38:758 (Oct.) 1929.

29. Details for this section have been published in Child Development, June 1938.

ture does not reveal any reason why the diabetic child should be especially bright, unless the disease is more frequently encountered among the higher socioeconomic classes. It is well known that the average intelligence quotient of the upper socioeconomic groups is above that of the average or lower groups.[30] It would, on the other hand, be reasonable to suppose that the nervous system might suffer from the disturbed general metabolism in diabetes, at least until the disease is brought under control. An objective study made by Miles and Root [31] on some of Joslin's adult diabetic patients just before the advent of insulin substantiates this supposition, since they found a decrement of at least 15 per cent in memory and attention tasks.

Our diabetic group are distributed normally in regard to intelligence, as determined by the Stanford-Binet test (table 13). No relation was

TABLE 13.—*Intelligence Quotient Distribution of Sixty Diabetic Patients and Twenty-Eight Siblings*

| | Diabetic Children | | | | Siblings | | |
|---|---|---|---|---|---|---|---|
| I. Q. | M | F | Total | Percentage | M | F | Total |
| 140 and over..... | .. | 1 | 1 | 1.7 | 2 | .. | 2 |
| 130 to 140..... | 1 | 2 | 3 | 5.0 | .. | 1 | 1 |
| 120 to 130..... | 4 | 1 | 5 | 8.3 | 2 | 1 | 3 |
| 110 to 120..... | 3 | 5 | 8 | 13.3 | 3 | 2 | 5 |
| 90 to 110..... | 11 | 15 | 26 | 43.3 | 9 | 5 | 14 |
| 80 to 90..... | 3 | 7 | 10 | 16.7 | 1 | 0 | 1 |
| 70 to 80..... | 1 | 4 | 5 | 8.3 | .. | .. | .. |
| 50 to 70..... | .. | 1 | 1 | 1.7 | 1 | 1 | 2 |
| Total..... | 23 | 37 | 60 | | 18 | 10 | 28 |
| Medians..... | 102.63 | 95.34 | 99.5 | | Median = 106.25 | | |
| Means ..... | 103.50 | 98.90 | 100.65 | | Mean = 107.00 | | |

found between duration or severity of the disease on the one hand and intelligence quotient on the other. Reports from the children's parents and teachers indicated that they considered the diabetic children's ability and achievement to be approximately on a par with those of their siblings and also with those which they exhibited before the onset of the disease.

*Personality Rating.*[29]—Behavior of the diabetic children as observed by a trained psychologist or pediatrician during the test situation varied little, if any, from the average, and there were no consistent trends. Moreover, in scores on the Woodworth-Cady Psychoneurotic Inventory, the diabetic subjects were approximately equal to their siblings.

30. Terman, L. M.: Genetic Studies of Genius, Palo Alto, Calif., Stanford University Press, 1926, vol. 1. Terman, L. M., and Merrill, M. A.: Measuring Intelligence, Boston, Houghton, Mifflin Company, 1937. Freeman.[26a]

31. Miles, W. R., and Root, H. F.: Psychologic Tests Applied to Diabetic Patients, Arch. Int. Med. **30**:767 (Dec.) 1922.

SUMMARY

Data pertaining to body growth, intelligence, heredity, sex distribution and incidence of acute infections have been obtained from case studies and individual interviews of 60 juvenile diabetic patients. These have been compared with equivalent data from nondiabetic siblings and from diabetic subjects reported on by other workers.

The group of patients included in the study appear to be typical of the juvenile diabetic population of Minnesota and apparently representative of the general child population of the state as regards socioeconomic status, race and geographic distribution.

While one third of the patients reported having had some acute infection (other than the common cold) within six months of the onset of diabetes, the group has on the whole been as healthy as the nondiabetic siblings (except for acidosis and insulin reactions).

Limited measurements of this group of juvenile diabetic patients revealed no consistent or peculiar deviations from the average in height.

The diabetic children were significantly underweight only during the first six months of their disease.

In contrast to the superior intelligence shown by Joslin's diabetic children, the intelligence of the present group showed no deviation from the average and no significant deviation from that of their sibling controls or from the average of Minneapolis children. No characteristic abnormalities in personality were discovered.

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# INDIVIDUAL GROWTH RECORDS OF TWO HEALTHY GIRLS FROM BIRTH TO MATURITY

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"The growth of a child has a greater importance for growth physiology than the average growth curve of 100,000 children," according to Davenport.[1] Others glorify the longitudinal (individual) method to such an extent that it almost appears the mode of the moment to decry cross section (group) data. Obviously, each has its own place and value, and the present trend doubtless reflects the need for more and completer individual studies of growth. These are difficult to collect, particularly for the entire period of active growth. Thus, the first seriatim study, begun in 1759 and reported by Buffon in 1827,[2] was considered sufficiently important by Scammon [3] to be worth republishing in detail. In all the intervening years few individual studies have been published, and in these few characteristics were measured. To the list we can now add two new seriatim studies, which are noteworthy in the following respects:

1. The span covered, from birth to maturity, has few equals. The range of most series seldom amounts to eight years of the whole active growth period of two decades.

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From the Departments of Medicine and Pediatrics, Stanford University School of Medicine.

1. Davenport, C. B.: Curves of Growth, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1934, vol. 2, p. 207.

2. Buffon, G.: Oeuvres complètes de Buffon mises en ordre et précédées d'une notice historique par A. Richard, suivies de deux volumes sur le progrès des sciences par Cuvier, Paris, Delangle frères, 1827, vol. 11, p. 396. (This edition, unlike some others, was regarded by Scammon as "thoroughly authoritative." The observations, however, seem to have first appeared in print in 1777, according to Scammon.)

3. Scammon, R. E.: The First Seriatim Study of Human Growth, Am. J. Phys. Anthropol. **10**:329 (Sept.) 1927.

2. The frequency of observation is unique. That alone justifies publication in exhaustive detail, for such basic observations can be useful for studies beyond the scope of that reported here.

3. The completeness of the set of traits, besides height and weight, which were measured for one of the children is believed unique. The present paper, however, will treat only height and weight.

4. The racial and economic background was such as to start and support both subjects toward ideal girlhood.

5. The health of the subjects was guided year after year by the same physicians. This minimized the impediments which at times inhibit growth, sometimes severely. Furthermore, when such checks occurred this supervision made them known, thus enabling us to interpret fluctuations in growth on a surer basis than can be attained by students of loaned series of children they have never seen.

6. The courses of growth have in fact run along with unusual uneventfulness. This minimizes the need of making allowances for checks. Such allowances can hardly avoid a flavor of arbitrariness; nonetheless we shall make them on occasion, since we are attempting to ascertain essential action.

7. Standards based on similar material are much more reliable than those based on mixed material. For our 2 subjects, fortunately, such standards are at hand; they are based on the same racial-economic group (Gray and Ayres [4]).

8. The subjects are girls, with known menarcheal age. This permits evaluation of some recent assertions in the literature as to the value of this item in predicting growth, a problem fairly frequent in practice. For example, the statement of Key [5] that puberty begins with a rapid increase in height and weight has been amplified by valuable evidence on the relation of growth behavior to the onset of the catamenia in girls or to the age of appearance of axillary hair in boys. For this phenomenon the term "puberty," long used, seems worth keeping. "Maturity" has been used as a synonym by some; but we prefer to use that term, as it has long been and still is ordinarily understood, to include many other traits besides whatever may be taken as the sign of physical puberty. In other words, maturity means to us not the beginning of adolescence but its ending. Incidentally, types of growth pattern other

4. Gray, H., and Ayres, J. G.: Growth in Private School Children with Averages and Variabilities Based on 3,110 Measurings on Boys and 1,473 on Girls, from the Ages of One to Nineteen Years, Behavior Research Fund Monograph, Chicago, University of Chicago Press, December 1931.

5. Key, A.: On the Development of Puberty and Its Relation to the Health of the Student, Nord. med. Ark. **23**:13, 1891.

than pubertal, such as Scammon's [6] organ types, may prove even more useful in prediction; but these also we leave until another time.

## ORIGINAL RAW DATA

*Genetic History of Subject 1.*—J. G. was born on Dec. 8, 1921, in Boston, of so-called old American stock. The family build history is shown in the tabulation: values are net, the metric values being precise and the others rounded off for the convenience of the reader.

| | Net Height | | Net Weight | |
|---|---|---|---|---|
| | Mm. | Ft. and In. | Kg. | Lb. |
| Father's father | 1,740 | 5 ft. 8 in. | 50.9 | 132 |
| Father's mother | 1,641 | 5 ft. 5 in. | 55.1 | 121 |
| Mother's father | 1,819 | 6 ft. | 104.5 | 230 |
| Mother's mother | 1,625 | 5 ft. 4 in. | 70.6 | 155 |
| Father | 1,819 | 6 ft. | 76.2 | 168 |
| Mother | 1,659 | 5 ft. 5 in. | 60.0 | 132 |
| Elder brother at 22 years | 1,870 | 6 ft. 2 in. | 82.1 | 182 |
| Second brother at 21 years | 1,938 | 6 ft. 4 in. | 89.8 | 198 |

Such genetic data have been used to predict a child's size at maturity. Pearson [7] devised an elaborate system, which we shall not use here; we shall only convert the father's measurements to female equivalents by Parson's rule, female = male times 12/13 (i. e., 0.923), giving for this child's father the female equivalents 1,679 mm. and 70.3 Kg. The ancient rule of thumb that the child will be like a hypothetic midparent gives the following simple predictions:

Predicted stature: (father 1,679 mm. + mother 1,659 mm.)/2 = child 1,669 mm.

Predicted weight: (father 70.3 mm. + mother 60.0 mm.)/2 = child 65.2 Kg.

These figures represent good guesses, since in fact at the age of 17 years the girl had the following measurements:

Actual stature: 1,674 mm., the error in guessing amounting to 0.3 per cent.

Actual weight: 59 Kg., the error in guessing amounting to 10.5 per cent.

*Genetic History of Subject 2.*—H. C. C. was born on March 20, 1921, also of old American stock (three grandparents were born in this country and one in Scotland). Her family build history, like her own build measurements, is less complete than that of the first child but is instructive. She has no sisters or brothers.

| | Net Height | | Net Weight | |
|---|---|---|---|---|
| | Mm. | Ft. and In. | Kg. | Lb. |
| Father's father | 1,727 | 5 ft. 8 in. | 68.9 | 152 |
| Father's mother | 1,549 | 5 ft. 1 in. | 45.8 | 101 |
| Mother's father | 1,753 | 5 ft. 9 in. | 64.4 | 142 |
| Mother's mother | 1,575 | 5 ft. 2 in. | 45.8 | 101 |
| Father | 1,778 | 5 ft. 10 in. | 68.0 | 150 |
| Mother | 1,575 | 5 ft. 2 in. | 61.2 | 135 |

The midparent rule predicts for her height 1,608 mm. and for her weight 62.0 Kg., as compared with actual measurements at the age of 17 years, 1,694 mm. and 62.6 Kg., respectively, the estimates being in error by 5.1 per cent for height and 1 per cent for weight.

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6. Scammon, R. E.: The Measurement of the Body in Childhood, in Harris, J. A.; Jackson, C. M.; Paterson, D. G., and Scammon, R. E.: The Measurement of Man, Minneapolis, University of Minnesota Press, 1930, p. 193.

7. Pearson, K.: On a New Theory of Progressive Evolution, Ann. Eugenics **4**:5 (April) 1930.

*Serial Observations.*—The series of ages, heights, weights and notes, listed monthly up to the age of 1 year and semiannually thereafter, together with other data for these children, are recorded in appendixes A and B. As presentation of the details would be difficult, portions of the data will be abstracted and treated, one at a time.

*Smoothness of the Course of Growth.*—We have plotted not only the heights listed in the appendixes (charts 1 and 2) but a vast quantity

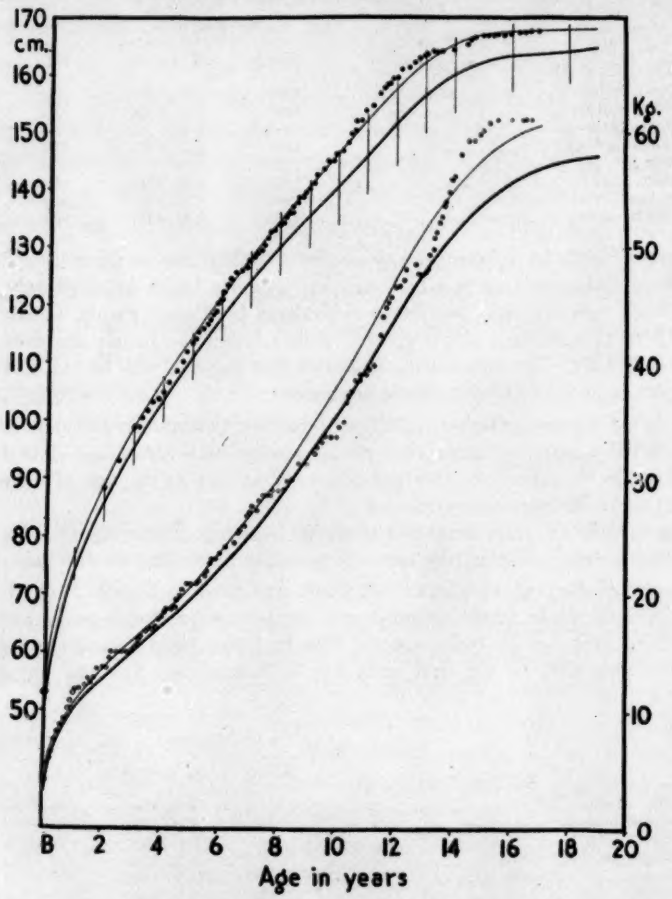


Chart 1.—Heights and weights of J. G. from birth to maturity. Solid dots indicate the subject's heights and circles her weights. Heavy lines are based on means for private school girls. Light lines show prediction standard 1.

of interim observations which we refrain from reporting. The interim points naturally show fluctuations. The significance of these short time variations for the study of growth rates has been discussed previously

(Bayer and Gray [8]); here we shall merely add that the diagram published in the previous report, which was also for J. G., shows that rates calculated for three month intervals fluctuate enormously, even in health: For instance, from her third to her fourth birthday the relative rate was 6 per cent over the whole year, but in the successive quarters of that year it showed the following variations: 1.6, 11.8, 4.7 and 5.0

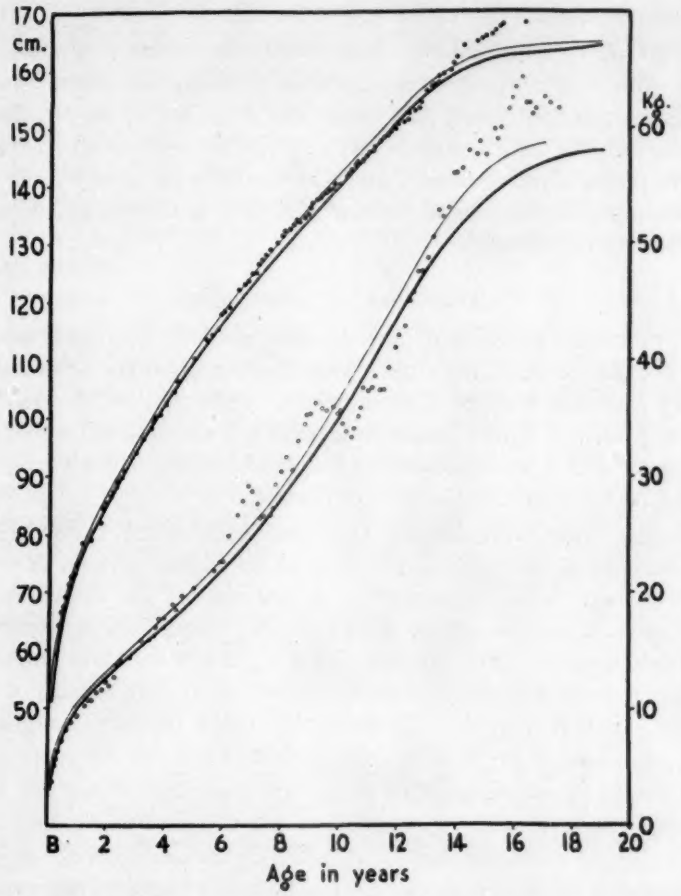


Chart 2.—Heights and weights of H. C. C. from birth to maturity. Solid dots indicate the subject's heights and circles her weights. Heavy lines are based on means for private school girls. Light lines show prediction standard 1.

per cent. Hence we conclude that short term observations are often only confusing in a study of growth, except as they confirm the reliability

8. Bayer, L. M., and Gray, H.: Pituitary Dwarfs: Their Growth and Treatment [fig. 4], California & West. Med. **47**:228 (Oct.) 1937.

of the semiannual points, which are those we used to establish each child's curve.

*Absolute Stature Versus Rates.*—In this paper we shall deal only with the straightforward orientation of absolute stature, and we shall postpone further discussion of yearly rates, either as absolute gains in millimeters or as relative rates in percentages, for that "differential" treatment, while worth pursuing, is unnecessarily complex for our present purposes.

*Methods of Comparison.*—We wish to determine how closely each girl's growth conformed to expectations furnished by several standards and to use this conformity as a test of the suitability of the standards for prediction. We have therefore (*a*) to define our criterion of agreement, (*b*) to define some standards and (*c*) to test each child by the chosen criterion against the several standards so that finally we can choose one standard to recommend.

## CRITERION OF AGREEMENT

A numerical criterion of agreement is needed. Naturally one starts with the difference of the child's measurement from the standard value, say by a certain number of millimeters. This absolute deviate is hard to interpret, for 5 mm. means little with a large dimension like stature and much with a small dimension like hand length. Clearly, the deviate should be translated into a relative deviate.

*Sigma Scale.*—The deviate (conventionally called x) is divided by the standard deviation ($\sigma$), which gives the sigma deviate, or standard score ($x/\sigma$). This, no matter what the size of the dimension or in what units it was measured, can be reliably interpreted by reference to a probability table. For example, if for a girl $x/\sigma = 2$, one refers to the table and finds that 977/1,000 of the population are smaller than this subject, in short, that she is at the ninety-eighth percentile, which means that only about 2 per cent of normal girls of her age are more extreme than she is. Such sigma scale values are important to any one wishing to enter into estimates of probability and will in fact be used later in this paper to construct several standards. But as a criterion they are inconvenient to the physician, who seldom has heard of the probability table or does not have one at hand. We therefore turn to a less significant but simpler method.

*Percentage Deviation from Standard.*—The deviation in millimeters is divided by the mean for the age to obtain the deviation as a percentage, plus or minus, larger or smaller. This criterion may be used to define the relative position or size not only of an individual but sometimes of a group. The propositus is usually compared with a general average

but sometimes with an average derived from a group at the larger or smaller end of the scale. The latter, less usual, method is here mentioned because it has been used by some writers on growth as affected by puberty and also because it can easily lead to confusion and even error. This may be seen readily in the important evidence summarized in the sections on the early pubescent versus the late pubescent and the early pubescent versus the midpubescent group.

*Early Pubescent Versus Late Pubescent Group.*—The importance of a child's stage of pubescence in relation to placement in class, in athletics and in social contacts is today established, though often neglected. Likewise the importance of pubescence in assessing a child's growth has been documented in several valuable papers. Some authors have seemed to regard pubertal age as the dominant factor in a standard; we wish to determine whether this enthusiasm for a new-found method is overexclusive. To illustrate, we first present some excerpts from two valuable sources.

In regard to weight, Crampton [9] stated that at the age of 15.75 years postpubescent children are 34 per cent heavier than prepubescent, and this figure we confirm from his data. Similarly Shuttleworth [10] stated that at the ages of 11 and 12 years the group menstruating before the age of 11 years and 6 months average 50 per cent heavier than the group menstruating after the age of 14 years and 5 months; this figure, however, we are unable to confirm. For example,[11] for the age of 11 years: (37.66 pounds — 29.29 pounds)/29.29 = only a 13 per cent gain, and for the age of 12 years (43.60 pounds — 32.09 pounds)/32.09 = only a 14 per cent gain.

Concerning stature, Crampton [9] wrote: "The mature are 10 per cent taller." This value, taking his data for weight at the age of 15.75 years, we find slightly exaggerated, since (1,619 mm. — 1,499 mm.)/1,499 = only an 8 per cent gain. Similarly, Shuttleworth [12] stated that at the ages of 11 and 12 years the group menstruating before the age of 11 years and 6 months averaged 12 per cent larger in linear measurements than the group menstruating after the age of 14 years and 5 months. This value again we fail to confirm from his data; [13] for

9. Crampton, C. W.: Physiological Age—A Fundamental Principle, Am. Phys. Educ. Rev. **13**:141, 214, 216, 268, 281 and 345, 1908; Anatomical or Physiological Age vs. Chronological Age, Pedagog. Seminary **15**:233 (June) 1908.

10. Shuttleworth, F. K.: (*a*) Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monographs of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 5 (serial no. 12), p. 134; (*b*) Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen, ibid., 1938, vol. 3, no. 5 (serial no. 18), p. 1.

11. Shuttleworth,[10a] p. 223.

12. Shuttleworth, [10a] p. 134.

13. Shuttleworth,[10a] p. 220.

the age of 11 years we calculate that (1,426 — 1,335 mm.)/1,335 = a 7 per cent gain, and for 12 years (1,488 — 1,382 mm.)/1,382 = only an 8 per cent gain. These arithmetic points we mention merely by the way. More general objections may be raised to the illustrated method of referring the percentage to a contrasted group rather than to the general average, at least for the immediate purpose, which is to assess the amount of error which one may hope to avoid by grouping girls according to menarcheal age.

Too small a number of subjects results from taking extreme classes in an eightfold partition (A to H); e. g., inspection of Shuttleworth's [13] data reveals that of the 123 children 11 years old who were measured, about 9 per cent fell in each of the two groups (A and H) compared, making together only 18 per cent dealt with out of all the girls at that age; i. e., the proportion of the whole age sample used is too small to be relied on. This objection can be obviated by pooling Shuttleworth's results into only three groups, such as those used by other recent writers along these lines:

I. ABCD gives for prepubescent children 64/123, or 52 per cent.
II. EF gives for pubescent children 43/123, or 35 per cent.
III. GH gives for postpubescent children 16/123, or 13 per cent.

On this basis, comparison of early and late pubescent groups would deal with 65 per cent (52 per cent + 13 per cent) instead of 18 per cent of the girls used in the original comparison (in the row taken for illustration, namely, the row for 11 year old children).

Comparison between extreme classes, whether for menarcheal age or for any other classification, is a still more dubious procedure. It emphasizes (consciously or unconsciously) extreme variants in the distribution. Hence statisticians deprecate the too common use of the difference of the ends of range of extreme individuals and themselves have for years interpreted data for individuals in terms of deviation from the average.

Even biologically, the extremes may be viewed askance as often being (whether or not this is recognized by adequate examination of the subject) no longer normal variates but pathologic inclusions.

*Early Pubescent Versus Midpubescent Group.*—This not only is the center of gravity of this classification but is much the same as the general average. Following this alternative method of comparison, we should recast the first illustration quoted from Crampton to read: The early puberty group are 19 per cent (not 34 per cent) heavier than the general run. This criterion seems sounder and therefore will be used in this paper; it may be defined as the deviation of the girl studied from the average height for age, expressed in percentage above that average.

The next question concerns the choice of standard best used to predict that average.

### STANDARDS

We want averages based on children of like sex, race, economic stratum and age, together with some adjusting factor either for physiologic age or for individual rank relative to other children of the same chronologic age. For the sex-race-stratum-age conditions of our 2 subjects most standards in print are too low. This fact conveniently limits the number worth trial. We shall consider the following standards:

*Private School Means.*—Average statures for age in girls, as presented by Gray and Ayres,[4] are shown in chart 1, in the upper heavy curve. Most standards are lower and therefore not suited as bases of comparison for our 2 girls, but the recent Cleveland Inquiry Series of Simmons and Todd [14] agrees so strikingly that their values at birth, 0.25, 0.50 and 0.75 years, have been used to extend our curve at the lower end back to birth.

*Individual Position Among Girls of the Same Age, Percentiles.*—Simmons and Todd [14] concluded that from the second to the thirteenth birthday a child's rank in the group stature distribution is stable and consistent from year to year. Others have judged that the consistency of build persists later still, apart from occasional exceptions in the later teens. Such inconvenient variations in rank for some individuals at successive ages has been shown by Baldwin [15] and recently has been neatly demonstrated by Dearborn, Rothney and Shuttleworth.[16] Shuttle-

14. Simmons, K., and Todd, T. W.: Growth of Well Children: Analysis of Stature and Weight, Three Months to Thirteen Years, Growth **2**:93 (Aug.) 1938.

15. Baldwin, B. T.: The Physical Growth of Children from Birth to Maturity, Iowa City, University of Iowa, 1921.

16. Dearborn, W. F.; Rothney, J. W. M., and Shuttleworth, F. K.: Data on the Growth of Public School Children, Monographs of the Society for Research in Child Development, National Research Council, 1938, vol. 3, no. 1, p. 136. Incidentally, the memoir by Dearborn and Rothney furnishes an important discussion of the desirability of predicting normal weight from body measurements by multiple regression equations, and they make such a calculation. For those interested in this aspect, the following chronologic collection of references may be useful: Gray, H.: Weight, Body Diameters and Age: Correlation Coefficients, Proc. Soc. Exper. Biol. & Med. **25**:384 (Feb.) 1928; The Relation of Weight to Stature, Bi-Cristal Diameter and Age, Biometrika **20A**:299 (Dec.) 1928. Highsmith, J. A., and Sorenson, D.: A Tentative Weight-Prediction Formula, Am. Phys. Educ. Rev. **33**:448 (Sept.) 1928. Miles, W. R.: Human Body-Weight: Correlations, Science **58**:382 (Oct. 19) 1928. Rosenow, C.: Weight and Skeletal Build, Am. J. Orthopsychiat. **3**:55 (Jan.) 1933. Allen, R. L.: Weight Deviation and Health in a College Group, Research Quart., Am. Phys. Educ. A. **7**:89 (Oct.) 1936 (31 references).

worth, in 1937 presented curves for 10 girls which show how uniform individual creatures can be in growth pattern; their statures of course differ but the changes in rank do not seem disturbing.

In our 2 cases the extent of fluctuations in rank as the girls grew older is shown for stature in table 1; they are hardly remarkable.

It should be understood that a child's position, though it may rise or fall at some ages, is on the whole sufficiently constant to suggest the method of adjusting standards by individual position, as we shall explain. However, the position as just defined numerically by a percentile, while used at times and simpler in concept, is less convenient statistically than when defined by a multiple of the standard deviation, or sigma; hence the use of the sigma scale. Before applying this we must discuss standard deviations.

TABLE 1.—*Fluctuation in Percentile Position at Successive Ages* *

| Age, Yr. | J. G. | H. C. C. | Age, Yr. | J. G. | H. C. C. |
|---|---|---|---|---|---|
| Newborn | 93 | 14 | 9 | 75 | 56 |
| 1 | .. | 43 | 10 | 83 | 54 |
| 2 | 80 | 46 | 11 | 86 | 48 |
| 3 | 78 | 32 | 12 | 85 | 44 |
| 4 | 59 | 41 | 13 | 80 | 48 |
| 5 | 68 | 44 | 14 | 73 | 65 |
| 6 | 73 | 56 | 15 | 73 | 72 |
| 7 | 74 | 58 | 16 | 78 | 88 |
| 8 | 69 | 58 | 17 | 77 | 86 |
| Average | | | | 76.7 | 52.9 |
| Standard deviation | | | | 8.0 | 18.0 |
| Standard error of average | | | | 2.0 | 4.0 |

* Referred to mean statures of Gray and Ayres.

*Standard Deviations.*—The variation of different girls of a given age around the average is diagrammed in chart 1 by vertical bars, each representing plus or minus one standard deviation, the range covering the central 68 per cent of heights in each age group. The bars show in the first place that the child in question is well within the range of normal values. But the standard deviations are of more extensive use. The private school values are plotted against age in chart 3; they are somewhat irregular, owing to fluctuations of sampling; indeed the irregularities are sufficiently marked to suggest that the original values for the standard deviation are imperfect estimates of the true values for the population at those ages, especially below the age of 4 years. Fortunately Simmons and Todd [14] have presented their Inquiry Standard Series as applied to Cleveland children. As they properly anticipated from their similar race-economic selection, their results agreed beauti-

fully with the values for private school girls, within the errors to be expected by chance sampling, in certain characteristics and at certain ages. For the present purpose we note that their standard deviations agree accurately with ours at the ages of 6.0 and 5.0 years and provide valuable and fairly smooth values at half-year intervals back to birth. These values were inserted in chart 3, the trend shown was then

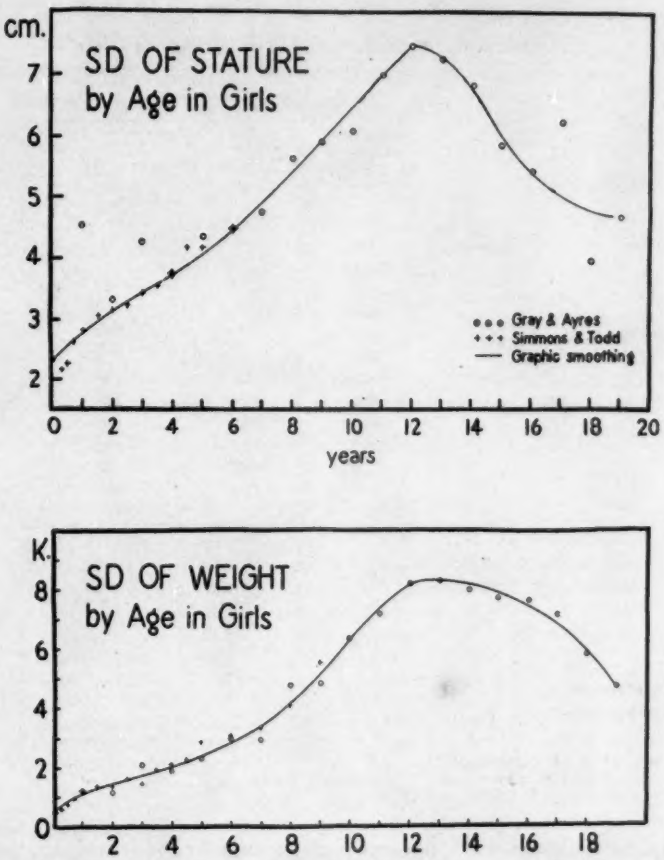


Chart 3.—Standard deviation for girls at any given age. This shows how much the standard deviation varies at different ages, even after the irregularities of the original calculated values have been ironed out by a smoother curve.

fitted by eye, and from it smoothed values for sigma were read off and listed in table 2, column 2. They define the variation in each age group of girls (*a*) whose ages varied between half a year younger and half a year older than the central age stated and (*b*) who often were measured at only two ages. It is interesting therefore to compare with our stand-

ard deviations the recent values of Richey [17] in table 2, column 3, which differ in pertaining to girls (*a*) who had ages within a few days of the central age stated and (*b*) who were measured often at more than two ages; his standard deviations accordingly might be expected to show a distinct reduction in variance. The changes, a reduction being indicated by a minus sign, are shown in absolute differences of millimeters in column 4 and in percentages of our values in column 5. The reduction

TABLE 2.—*Standard Deviation of Stature in Girls*

| | Sigma | | Deviation | |
|---|---|---|---|---|
| Central Age, Yr. | Smoothed Values of Gray and Ayres * | Values of Richey* | R — GA,† Mm. | R — GA / GA,‡ % |
| (1) | (2) | (3) | (4) | (5) |
| Newborn | 23.4 | | | |
| 1 | 27.8 | | | |
| 2 | 31.5 | | | |
| 3 | 34.2 | | | |
| 4 | 37.5 | | | |
| 5 | 40.5 | | | |
| 6 | 44.7 | 50.0 | 5.3 | +10.60 |
| 7 | 49.0 | 51.6 | 2.6 | + 5.04 |
| 8 | 54.0 | 52.1 | −1.9 | − 3.65 |
| 9 | 59.0 | 58.9 | −0.1 | − 0.17 |
| 10 | 65.0 | 66.5 | 1.5 | + 2.26 |
| 11 | 70.0 | 73.9 | 3.9 | + 5.28 |
| 12 | 74.7 | 76.7 | 2.0 | + 2.61 |
| 13 | 72.8 | 69.1 | −3.7 | − 5.35 |
| 14 | 67.5 | 58.4 | −9.1 | −15.58 |
| 15 | 60.0 | 52.6 | −7.4 | −14.07 |
| 16 | 54.1 | 50.5 | −3.6 | − 7.13 |
| 17 | 50.0 | 49.5 | −0.5 | − 1.01 |
| 18 | 47.8 | | | |
| 19 | 49.6 | | | |
| Total reduction | | | | −21.17 |
| Average reduction | | | | − 1.76 |

* See page 14 of monograph.[17]
† Value of Richey minus value of Gray and Ayres.
‡ The minus sign indicates reduction.

amounted to around 15 per cent at the ages of 14 and 15, and some reduction occurred at 7 ages. However, in 5 of 12 age comparisons there was no reduction; this lack of a uniform reduction suggests that the theoretic advantages of measurements like Richey's are not as great as anticipated; specifically, the average of the 12 comparisons, with regard to sign, on the whole showed reduction but by only 1.8 per cent of our values.

17. Richey, H. G.: The Relation of Accelerated, Normal and Retarded Puberty to the Height and Weight of School Children, Monograph of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 1 (serial no. 8).

All in all, then, the smoothed values for sigma in column 2 are put forward as representative standards of variation in stature among girls such as our subjects and will be valuable in estimating the position of each child with regard to those of other girls of her age.

TABLE 3.—*Paradigm for Estimating a Child's Individual Deviate, or Sigma Position, Defining Our Prediction Standard and Testing the Error of Observation from Standard*

| | Stature | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Private School Standard | | Individual Deviate | | Prediction Standard | | Test of Error | |
| Age at Nearest Year | J. G., Mm. | Mean, Mm. | Standard Deviation Smoothed, Mm. | Absolute, Mm. | Relative | Adjustment, Mm. | Adjusted Mean Stature, Mm. | Observed Predicted, Mm. | Minus, % of P |
| | X | M | $\sigma$ | X − M = x | x/$\sigma$ | Estimated Individual x/$\sigma$ Times Col. $\sigma$ = a | M + a = P | X − P = p | 100 p/P |
| | | | | (2)—(3) | (5)/(4) | 0.76×(4) | (3)+(7) | (2)—(8) | (9)/(8) |
| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) |
| Newborn | 530 | 495 | 23.4 | 35 | +1.50 | 18 | 513 | 17 | +3.31 |
| 1 | ... | 754 | 27.8 | .. | ..... | 21 | 775 | .. | ..... |
| 2 | 880 | 854 | 31.5 | 26 | +0.83 | 24 | 878 | 2 | +0.23 |
| 3 | 985 | 959 | 34.2 | 26 | +0.76 | 26 | 985 | 0 | 0.00 |
| 4 | 1,044 | 1,035 | 37.5 | 9 | +0.24 | 28 | 1.063 | −19 | −1.79 |
| 5 | 1,130 | 1,111 | 40.5 | 19 | +0.47 | 31 | 1,142 | −12 | −1.05 |
| 6 | 1,208 | 1,181 | 44.7 | 27 | +0.60 | 34 | 1,215 | − 7 | −0.58 |
| 7 | 1,273 | 1,241 | 49.0 | 32 | +0.65 | 37 | 1,278 | − 5 | −0.39 |
| 8 | 1,333 | 1,307 | 54.0 | 26 | +0.48 | 41 | 1,348 | −15 | −1.11 |
| 9 | 1,400 | 1,359 | 59.0 | 41 | +0.69 | 45 | 1,404 | − 4 | −0.28 |
| 10 | 1,462 | 1,401 | 65.0 | 61 | +0.94 | 49 | 1,450 | 12 | +0.83 |
| 11 | 1,537 | 1,461 | 70.0 | 76 | +1.09 | 53 | 1,514 | 23 | +1.52 |
| 12 | 1,598 | 1,520 | 74.7 | 78 | +1.04 | 57 | 1,577 | 22 | +1.40 |
| 13 | 1,633 | 1,572 | 72.8 | 61 | +0.84 | 55 | 1,627 | 6 | +0.37 |
| 14 | 1,643 | 1,601 | 67.5 | 42 | +0.62 | 51 | 1,652 | − 9 | −0.54 |
| 15 | 1,666 | 1,630 | 60.0 | 36 | +0.60 | 46 | 1,676 | −10 | −0.60 |
| 16 | 1,671 | 1,629 | 54.1 | 42 | +0.78 | 41 | 1,670 | 1 | +0.06 |
| 17 | 1,674 | 1,639 | 50.0 | 35 | +0.70 | 38 | 1,677 | − 3 | −0.18 |

Sum of 17 values (col. 6), added with sign..... 12.83
Average..... 0.75

Estimates of individual average relative deviate x/$\sigma$:
- (a) At 5 yr..... = 0.47
- (b) Average of all 17 values..... = 0.75
- (c) Average 2 close values..... = 0.80
- (d) Average through 5 yr..... = 0.76

+7.72
−6.52

Sum of 17 values, added without sign. 14.24
Average..... 0.838

Estimates of prediction error in percentage of predicted stature:
- (1) Range..... = 0 to 3.3
- (2) All 17 yr..... = 0.838
- (3) Ages 6-17 yr... = 0.655

*Means Adjusted by Individual Sigma Position.*—The successive steps, though tedious, are made clear with the help of a paradigm, in table 3. Line by line, at each birthday, in column (1), we see our girl's height, in column (2); usually it was measured within a week before or after the exact date, but occasionally it was

interpolated by means of measurements taken a fortnight before or after the exact date. In column (3) are the private school girls' mean statures, based on ages from a half-year less to a half-year more than the ages stated. In column (4) are the standard deviations smoothed as in table 2.

The next vertical panel of the table shows the individual's deviate from the general average, absolutely in millimeters, in column (5), and relatively to sigma, in column (6); these indexes of our subject's $x/\sigma$ position naturally vary somewhat from age to age. As the girl grew older she diverged more and more from other girls to a maximum at her eleventh birthday, when the value was 1.09 $x/\sigma$; then she approached them again until, at the age of 17, her value was nearly the same as at her third birthday. From these varying values is formed a single estimate of her relative position. Values calculated by several methods are shown at the foot of the panel: Value (*a*) is the single value for the last year of observation before the prediction is made; in the present study, that means before the sixth birthday; that starting point is naturally indicated by the fact that some of the standards taken for trial have no values before that date. In J. G.'s case the value for the fifth year is $+0.47\ \sigma$, which is hardly representative of the run of her position values. Indeed, one would hardly expect a single year to give as representative a value as an average made up from several determinations. Value (*b*), the average for all 17 available ages (here $0.75\ \sigma$) would not serve as a general rule, however, since a patient usually comes to the pediatrician for growth problems only toward the end of the first decade. Value (*c*) is the average for the first pair of years that agree reasonably. In the case of this subject, the values for the ages of 2 and 3 years, $0.83\ \sigma$ and $0.76\ \sigma$, average $0.80\ \sigma$. This seems reasonably representative but still slightly less reliable than our next and final estimate. Value (*d*), the average of all the values up to the time of prediction, in this case 5 observations, is $+0.76\ \sigma$. This value appeals to us as the soundest.

In the third panel is derived our prediction standard 1. The chosen estimate, 0.76, is set up and multiplied successively by the smoothed sigma, the product being the necessary adjustment, written in column (7). Then, line by line, the adjustment is added to the original mean, giving the predicted or adjusted expected height for age in column (8). For instance, at the sixth birthday, $0.76 \times 44.7$ mm. = 34 mm.; 34 mm. + mean 1,181 mm. = predicted stature, 1,215 mm.

Before the close of this section, it may be noted that a child's sigma position with regard to stature is likely to be suitable for use only with bodily traits of Scammon's general organ type. Accordingly, when it is desired to treat head measurements one will probably require a sigma position based on the measurement in question or perhaps on the neural type. Since this type develops early in the life span, one would expect to obtain a satisfactory sigma position by the age of 1 or 2 years. Conversely, for bodily traits related to secondary sexual development, one probably needs a sigma position based on a later age, say the year of menarche.

The last panel tests the error between observation and prediction, to which we shall return after describing the other standards.

*Chronologic Age.*—This has been variously stated: (*a*) the age at the last birthday, i. e., from the birthday stated to the following birthday, in which case the age stated should be increased by one-half year to the midpoint of the period, before comparison according to the usual

practice; (*b*) the age at the nearest birthday, i. e., from one-half year less to one-half year more; this has become the usual practice; (*c*) the age at the "exact" birthday, i. e., within a week or so; this is clearly desirable but often impracticable; (*d*) the true age computed in years and decimal fractions (Toops;[18] Pearl and Miner[19]). These distinctions must be understood, for they may be important.

*Physiologic Age.*—For many years there have been recurrent slights on the use of chronologic age in predicting growth, together with valuable evidence in favor of the use of physiologic age. This has been variously termed maturity age, pubertal age, menarcheal age, pubic puberty, breast puberty, axillary puberty, bone age and the like, and has been variously defined. Some criteria are definite, as the first appearance of the catamenia. Some depend on stages, as shown by pubic hair: If this is absent, the subject is called immature or prepubescent; if "anything more than an abundant lanugo and less than a very well defined covering," pubescent; if "defined covering," postpubescent or mature (Crampton). The sequence is approximately as follows: (1) spurt in height, (2) at maximum of pubertal spurt, associated development of the breasts, (3) pubic hair, (4) axillary hair, (5) menarche and (6) closure of epiphyses with cessation of growth. Perhaps the most convenient criteria, in the light of present knowledge, are the menarche in girls and the appearance of axillary hair in boys. The two characters often appear about the same time, but axillary hair may precede the menarche by as much as three years, as in Nylin's[20] patient Gurli.

Growth prediction on the basis of pubertal age, whatever the criterion, is likely to prove at a disadvantage compared with prediction on other bases, because it must wait till puberty. That seldom occurs by the tenth birthday and usually comes later; e. g., about 0.8 per cent of girls have the menarche by the age of 10.0 years, and as girls are only half of all children, we can say that in only about 4 per thousand children will puberty start early enough to be useful clinically in growth prediction.

Reservations are also indicated to the supposition that the menarcheal age is an extremely definite characteristic of the individual, as

18. Toops, H. A.: Determining Chronological Age in Decimal Parts of a Year, J. Educ. Research **6**:438 (Dec.) 1922.

19. Pearl, R., and Miner, J. R.: A Table for Ascertaining Elapsed Time in Years and Decimals of a Year Between Any Two Dates, Quart. Bull., Milbank Mem. Fund **10**:151 (April) 1932.

20. Nylin, G.: The Physiology of the Circulation During Puberty, Acta med. Scandinav., 1935, supp. 69, p. 1.

shown by von Verschuer's [21] report on 14 pairs of one ovum twins, in which the difference in menarcheal age was said to be over a year in a fourth of the cases, the exact distribution of the differences being as follows:

| Difference in menarcheal age | Under 1 Mo. | 1-5 Mo. | 6-11 Mo. | 1 Yr. or More | Total |
|---|---|---|---|---|---|
| Number of pairs | 4 | 4 | 3 | 3 | 14 |

Again, menarcheal age in the same town is later the darker the color of the hair (Bolk; [22] Ley [23]), and stature, in the same locality, is greater in those with dark hair than in those with light (Tschepourkovsky; [24] MacConaill [25]).

The requirements for material for growth studies are severe and slighted often enough to warrant repetition:

1. Homogeneity as to racial origin.
2. Homogeneity as to economic status, with its implications in regard to health.
3. Homogeneity as to normality, i. e., freedom from children showing on medical examination an abnormal constitution or development retarded for any one of a number of causes.
4. Measurement without clothes.
5. Correct measurement.
6. Correct assessment as to pubertal age.
7. Correct assessment as to bone age.

*Three Menarcheal-Age Groups.*—Several authors have presented data useful for our purposes, namely means and standard deviations, divided into three groups: group I, early, or prepubertal; group II, pubertal, the one year period being centered on the birthday, or beginning with the birthday after which the girl had the menarche or the boy first showed axillary hair, and group III, postpubertal. Finer groupings have been used by some, but these will be omitted here because comparison would be rather difficult in view of the small numbers in many of the series reported, if due regard is held for natural fluctuations of sampling. Furthermore, we are impressed with the importance of avoiding multiple tables, such as

21. von Verschuer, O.: Die vererbungsbiologische Zwillingsforschung, Ergebn. d. inn. Med. u. Kinderh. **31**:109, 1927.

22. Bolk, L.: Untersuchungen über die Menarche, Ztschr. f. Geburtsh. u. Gynäk. **89**:364, 1925.

23. Ley, L.: Ueber die Menarche der Frau und ihre Beziehungen zur Pigmentation: Untersuchungen an Schulkindern der Stadt Mainz, Arch. f. Gynäk. **165**:489, 1938.

24. Tschepourkovsky, E.: Anthropologische Studien, Arch. f. Anthropol. **10**: 151, 1911.

25. MacConaill, M. A.: The Stature of Male Schoolchildren in Relation to Hair and Eye Colour, Ann. Eugenics **8**:117 (Jan.) 1938.

separate tables for three puberty groups wherever one exists today, and accordingly we wish to examine the feasibility of effective adjustment of existing tables. Let us therefore treat groups I, II and III as taken directly from different authors or as obtained by pooling their short age ranges, though the limits have not always been identical. For example, for the purpose of averaging material, the middle group has been defined differently with regard to the time of menarche: at or after the twelfth birthday and before the thirteenth (Stone and Barker[26]), and at or after the thirteenth and before the fourteenth (Boas;[27] Richey;[17] Shuttleworth, 1937). For our purpose the most suitable girls among these four sources are the laboratory school girls of Richey,[17] the standards of comparison being his mean stature for age for group I for our subject with early menarche, and for group III for our subject with late menarche. The numerical comparisons will be shown together later, after all the standards have been set. Let us assume that stature at each age of group II is approximately the same as that of the groups combined without regard to pubertal age. Let us define the greater tallness of group I over that of group II by calculating at each age the deviation (excess) of stature I from stature II and turning this excess into a percentage of stature II.

TABLE 4.—*Puberty Factors* *

| Age, yr..... | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Early group..... | 0.72 | 1.03 | 1.14 | 1.48 | 2.11 | 2.70 | 2.54 | 1.09 | 0.23 | 0.04 | −0.04 | 0.08 | −0.63 |
| Late group..... | −0.99 | −1.75 | −2.22 | −2.40 | −2.55 | −2.96 | −3.49 | −3.00 | −2.20 | −0.98 | −0.14 | −0.01 | −1.13 |

* Percentage by which the stature of the early menstrual group (before 13.0 years) exceeds that of the midmenstrual group (13.0 to 14.0 years) or by which the stature of the late menstrual group (after 14.0 years) falls short of that of the midmenstrual group. Values were calculated from data obtained from four sources.

Similarly, let us define the shortness of group III by calculating the difference (usually, but not always, a deficit, as will be discussed under the heading "Terminal Situation") between stature III and stature II and translating it into percentage of stature II. These percentages we shall term puberty factors. They have been computed from data obtained from the four sources just named. We may mention in passing that the curves for boys are unlike those for girls. For girls the curves of various authors differ, showing considerable irregularity (chart 4), as is so often the case when observations are not voluminous. Accordingly the four sets of calculations used are not reproduced but have been pooled at each age; each author's value has been weighted by his number of girls at that age, and the pooled results have been plotted as heavy black dots. Even the latter need smoothing before one can proceed; therefore we have drawn the heavy curves. For the early factors in the upper half of the diagram a curve is easily drawn to strike all points; for the late factors it has seemed better to draw by eye a trend through the field and from the trend to read some of the values as smoothed. Thus we

26. Stone, C. P., and Barker, R. G.: On the Relationship Between Menarcheal Age and Certain Measurements of Physique in Girls of the Ages Nine to Sixteen Years, Human Biol. 9:1 (Feb.) 1937. This article includes a good review.

27. Boas, F.: Studies in Growth, Human Biol. 4:307 (Sept.) 1932.

arrive at working values for respective chronologic ages, which are recorded in table 4. To use table 4 for a given child, consider the age at menarche: If the menarche occurs before the thirteenth birthday, use the set of early factors; if between the thirteenth and the fourteenth birthday, make no adjustment; if after the fourteenth, use the set of late factors. With the appropriate set of factors correct the private school means; the resulting values are denoted by the title at the beginning of this section. The actual plan of the calculations is analogous to that shown in the panel entitled Prediction Standard in table 3; specific results for J. G. at the age of 6 years are shown in table 5.

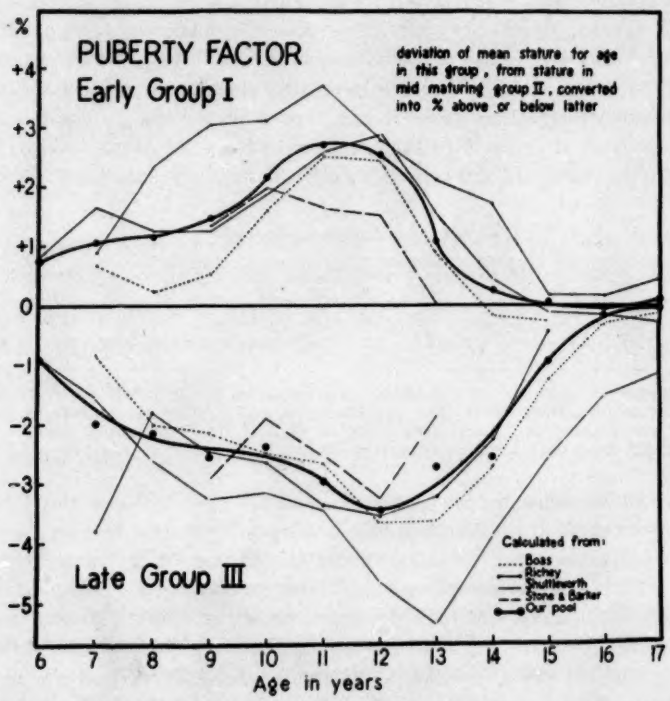


Chart 4.—Puberty factors. This indicates the percentage by which the stature of the early menstrual group (before 13.0 years) exceeds that of the midmenstrual group (thirteenth to fourteenth birthday) and by which the stature of the late group (after 14 years) falls short of that of the midmenstrual group.

*Prime or Terminal Situation.*—The reader may have noticed in table 4 in the row for early pubescent girls that in the late teens two minus values occur, which is to say that early pubescent girls when they reached the age of about 16 years became actually shorter than the midgroup. This question of the tendency of certain groups of children to a severe shift of rank at the end of growth has been discussed by a

few authors. For example, Boas [28] declared: "The social groups which show higher values of measurements do so on account of accelerated growth, and . . . cease to grow earlier than those whose growth is in the beginning less rapid, so that there is a tendency to decreasing differences between these groups during the last years of growth." Again, he stated: [27] "Acceleration or retardation within the same social group has apparently no influence upon adult stature." And, among those who judged differently, Stone and Barker [29] said: "Girls who mature at a young age show a tendency toward terminal inferiority in stature."

This reversal of rank is to be considered. In this connection it is necessary to comment on two recent statements. Shuttleworth, in 1938, declared: "Development is complete in the typical girl of 197 months." This age, in more convenient terms, is 16 years and 5 months, or 16.4

TABLE 5.—*Plan for Calculation of Standard with Puberty Factors, Showing Results for J. G.**

| Age, Yr. | Private School Means, Mm. | Puberty Factors, % | Prediction: Adjustment, Mm. | Prediction: Adjusted Mean Statures, Mm. |
|---|---|---|---|---|
| | M | P. F. | b | M + b |
| (1) | (3) | (6b) | (7b) | (8b) |
| 6 | 1,181 | +0.72 | +9 | 1,190 |

* See table 3.

years. Nearer the truth is this citation from Barker and Stone: [30] "The age at which mean growth ceases altogether cannot be stated, but appears to be beyond 20 years." But apparently these authors overlooked several published statements as to age prime for stature. True, most concern males. The lowest age is 21.5 years (Ruger and Stoessiger [31]); then come 24.9 years (Gray [32]) and with rising values, 28,

28. Boas, F.: Growth of Children, Science **5**:573 (April 9) 1897.

29. Stone, C. P., and Barker, R. G.: On the Relationships Between Menarcheal Age and Certain Aspects of Personality, Intelligence and Physique in College Women, J. Genetic Psychol. **45**:121, 1934.

30. Barker, R. G., and Stone, C. P.: Physical Development in Relation to Menarcheal Age in University Women, Human Biol. **8**:198 (May) 1936.

31. Ruger, H. A., and Stoessiger, B.: On the Growth Curves of Certain Characteristics in Man (Males), Ann. Eugenics **2**:76 (April 27) 1927.

32. Gray, H.: Body-Build in Illinois Convicts with Special Reference to Age, J. Crim. Law & Criminol. **25**:554 (Nov.-Dec.) 1934.

30 and 35 years (Quetelet,[33] Lélut,[34] Gould,[35] Hrdlička,[36] Reed and Love [37] and Hrdlička,[38] the last being an especially valuable article). For women the lowest prime is 17.5 years (Elderton, Moul and Page [39]); then come the ages from 22 to 29 years (Hrdlička [36]). For college women the following evidence on growth between admission and later examination is important:

| | | |
|---|---|---|
| Baldwin,[15] 1921 | 1,167.5 to 1,214.1 mm. | in 4 yr., or 1.2 mm. per yr. |
| Young,[40] 1928 | 1,633 to 1,641 mm. | in 3 yr., or 2.7 mm. per yr. |
| Gould,[41] 1930 | 1,154.9 to 1,176.6 mm. | in 4 yr., or 5.4 mm. per yr. |

The differences in rate growth are amazing. Furthermore, the later the publication, the greater the rate. More evidence on girls of college age is clearly needed. Meantime one must remember that when a stature curve flattens into a plateau in the later teens it may approximate the adult level, sufficiently well for many purposes, no doubt; but it is not certainly final, for there is often subsequent growth, slight on the average but as much as an inch (2.5 cm.) in occasional persons.

Of our 2 subjects, neither was short; the one with late menarche did not reach a plateau in statural growth till later than the one with early menarche and now exceeds her 1 cm. These facts agree with the view quoted from Stone and Barker, but we should like to amend their words. Since the early pubescent child by the age of 17 years had the position of $+ 0.70\,x/\sigma$, i. e., the 76 percentile, she has clearly "no

33. Quetelet, A.: Sur l'homme et le développement de ses facultés, ou essai de physique sociale, Bruxelles, L. Hauman & Cie, 1836.

34. Lélut, F.: Recherches pour servir à la détermination de la taille moyenne de l'homme en France, Paris, Bourgogne & Martinet, 1841.

35. Gould, B. A.: Investigations in the Military and Anthropological Statistics of American Soldiers, New York, United States Sanitary Commission, 1869.

36. Hrdlička, A.: The Old Americans, Baltimore, Williams & Wilkins Company, 1925.

37. Reed, L. J., and Love, A. G.: Biometric Studies on United States Army Officers—Somatological Norms, Correlations, and Changes with Age, Human Biol. **4**:509 (Dec.) 1932.

38. Hrdlička, A.: Growth During Adult Life, Proc. Am. Philos. Soc. **76**:847, 1936.

39. Elderton, E. M.; Moul, M., and Page, E. M.: On the Growth Curves of Certain Characters in Women and the Interrelationship of These Characters, Ann. Eugenics **3**:277 (Oct.) 1928.

40. Young, M.: Age of Full Stature in the Female, Am. J. Phys. Anthropol. **12**:285, 1928.

41. Gould, H. N.: The Physique of Women Students at Newcomb College of Tulane University: I. Stature and Weight, Research Quart., Am. Phys. Educ. A. **1**:1 (Oct.) 1930.

terminal inferiority in stature," and so the statement might well read: Girls who mature late may hope to shoot up to a terminal superiority of stature.

*Means Adjusted by Individual's Deviation from Average Menarcheal Age, Measured in Years.*—Instead of group correction, let us try a correction based on the individual's age at the first menses, as compared with the average menarcheal age of girls of similar racial-economic selection; if the girl matures early the

TABLE 6.—*Tests of J. G.'s Stature Against All Standards*

| Order of Merit | Error in Percentage | Standard |
|---|---|---|
| 1 | 0.655 | Private school means adjusted by individual stature relative deviate, assumed to be $+0.76\ x/\sigma$ |
| 2 | 0.864 | Private school means adjusted by individual menarcheal age relative deviate, $x/\sigma$ |
| 3 | 1.58 | Private school means adjusted by individual menarcheal age absolute deviate, mm. |
| 4 | 1.71 | Private school means adjusted by bone age relative deviate, assuming standard deviation of bone age as 1.66 years |
| 5 | 2.05 | Private school means adjusted by early group puberty factor |
| 6 | 2.57 | Early maturing group of Richey |
| 7 | 2.97 | Private school means adjusted by individual bone age absolute deviate, mm. |
| 8 | 3.17 | Private school means unadjusted |
| 9 | 3.63 | Private school means adjusted by individual bone age relative deviate, assuming standard deviation of bone age to be 1.17 years |
| 10 | 5.21 | Private school mature value adjusted by percentages expected at each age, according to Brody |
| 11 | 11.41 | Private school means adjusted by individual bone age relative deviate, assuming standard deviation of bone age to be 0.50 year |

TABLE 7.—*Test of H. C. C.'s Stature Against Various Standards*

| Order of Merit | Error in Percentage | Standard |
|---|---|---|
| 1 | 1.08 | Private school means adjusted by individual stature relative deviate assumed to be $+0.18\ x/\sigma$ |
| 2 | 1.30 | Private school means unadjusted |
| 3 | 3.04 | Private school means adjusted by late group puberty factor |
| 4 | 4.60 | Private school means adjusted by individual menarcheal age absolute deviate |
| 5 | 4.72 | Late maturing group of Richey |
| 6 | 4.99 | Private school means adjusted by individual menarcheal age relative deviate in mm. |

correction will be an addend; if late, a subtrahend. First an average must be chosen as base of reference; we take that of Stone and Barker, namely, 13.09 years. Then the work-sheet is analogous to that already described for standard I in the paradigm of table 3, in the panel headed Prediction Standard. Calculate how much the child's menarcheal age is advanced (or retarded) in years and hundredths of years; e. g., the average menarcheal age, 13.09 years, minus J. G.'s menarcheal age, $12.00 = +1.09$ years of advance, the constant. Add (or substract if the menarcheal age is retarded) this constant to the age 6 years: 6.00 years + 1.09 years = 7.09 years. With this adjusted age enter a curve of private school means and read predicted stature, 1,250 mm. (against which we shall later compare a child's actual height at the age of 6); similarly adjust the next age, with the

same constant, 7 years becoming 8.09 years, for which we read from the curve the predicted stature 1,308 mm., and so on; the set of predictions we define as in the title of this section.

*Means Adjusted by Individual's Deviation from Average Menarcheal Age, Measured on Sigma Scale.*—Instead of the absolute deviate in years, set up in the previous standard, let us try the relative deviate, that is, the deviate expressed in multiples of the standard deviation of menarcheal age. For this value we choose Stone and Barker's figure, 1.17 years. Divide the child's advancement in years by this standard deviation of menarcheal age; e. g., continuing with the child instanced in the last section: 1.09 years/1.17 years = x/SD = 0.932; this is the individual factor wanted. Let us assume that a child of this menarcheal age position relative to that of other girls will have the same relative position in statural age. Therefore, set up the factor, and multiply by the smoothed sigma of stature at the age of 6 years, 44.7 mm., getting 42 mm. Add this to the private school stature mean for the age of 6, namely, 1,181 mm., getting the predicted stature, 1,223 mm. Write this down and repeat for each successive age, using the respective stature sigma but the constant individual menstrual factor; the resulting column of predicted stature we define as in the title of this section.

*Means Adjusted for Deviation of Bone Age from Chronologic Age, Measured in Years.*—Let us assume that as the roentgen age is advanced so is the statural age. Calculate how far the child's bone age is advanced (or retarded) over her chronologic age in years and hundredths of years, calling this the individual bone age constant; e. g., for J. G. at the age of 12.00 years the bone age was 10.00 years, which gives the constant + 2.00 years. Add this constant to the age 6 years, getting 8.00 years; with this adjusted age enter the curve of private school means and read predicted height, 1,307 mm. Similarly adjust the next age, with the same constant addend, age 7 being thus adjusted to age 9.00, for which is read another predicted height, 1,359 mm., and so on; this set of predictions is denoted as in this section's title.

*Means Adjusted for Deviation of Bone Age from Chronologic Age, Measured on Sigma Scale.*—Instead of the absolute deviate in years set up in the preceding section, let us try the relative deviate, that is, as expressed in multiples of the standard deviation of bone age. For this the true value appears still uncertain, so we shall try several estimates: (*a*) 1.66 years, (*b*) 1.17 years (i. e., the standard deviation of menarcheal age), (*c*) 0.75 year and (*d*) 0.50 year.

Divide the absolute bone age deviate of the previous section by the chosen estimate of standard deviate for bone age; e. g., 2.00 years/1.66 = x/$\sigma$ = 1.20; call this the individual relative bone age deviate. Assume that a girl of this bone age position relative to that of other girls will have the same relative position in statural age. Accordingly, set up the relative deviate, multiply by the smoothed sigma of stature for the age of 6 years, 44.7 mm., which gives 54 mm. Add this to the mean stature for the age of 6, namely, 1,181 mm., obtaining the predicted stature, 1,235 mm. Write this down and repeat for each successive age, multiplying the respective stature sigma by the constant relative bone age deviate; the resulting column of predicted statures is labeled as in the title to this section.

*Statures for Various Ages Predicted as Percentages of Mature Stature.*—Brody's [42] "percentages of mature value" were read off from his graph, one for

42. Brody, S.: Growth and Development with Special Reference to Domestic Animals: IX, Research Bulletin 104, University of Missouri, College of Agriculture. Agricultural Experiment Station, June 1927, p. 23.

each age. As with other methods, we took the child's measurement at available ages up through the fifth birthday and divided each by Brody's percentage for that age to predict from each a mature value; the mean of these values was designated as *A*. The result was 1,829 mm., an amazing height. However, with that estimate as a base of reference, it was multiplied successively by Brody's percentages to get the predicted stature for each age.

*Means of Early Maturing Group of Richey.*—This set of means was obtained directly from his monograph, his group being compared with our early maturing subject.

TEST OF ERROR

*Method.*—We now return to our paradigm, in table 3. Its successive columns have already been explained, ending with column (8), the predicted statures of standard 1. We must now explain the final panel, headed Test of Error. For this test we then take the child's observed stature, in column (2), and subtract the corresponding predicted stature, in column (8), to get the absolute deviation in millimeters, in column (9); then in order to obviate the changing absolute height we divide the absolute deviation by the predicted stature, giving in the final column (10), the percentage of deviation from expectation, a plus sign showing that the child is taller than predicted and a minus sign that she is shorter.

Inspection of this column affords these conclusions: The percentage of prediction error varies from age to age, as expected; it happens to run from a maximum of 3.3 per cent at birth down to a minimum of 0 at the age of 3 years. The whole series of 17 values is not of primary interest here, because many standards do not permit comparisons below the age of 6 years; in passing we merely note that the 7 plus errors add to 7.72 and the 9 minus errors to 6.52 per cent; i. e., the values are nearly identical, which suggests a satisfactory prediction; the average error was 0.84 per cent. Primary interest attaches to the 12 yearly ages, 6 to 17 years inclusive, which are available for comparison in all standards; for this range there were 5 plus errors, adding to 4.18 per cent, and 7 minus errors, adding to 3.68 per cent; addition without regard to sign yields 0.655 per cent. Proceeding in the same way, we get for each of the other standards a similar average prediction error. This convenient method of testing accuracy has been adopted by a number of writers, e. g., Scammon and Calkins.[43]

*Results.*—Stature: How now do our 2 subjects agree with the various standards? For stature, the errors as arranged separately for each child in order of magnitude are given in tables 6 and 7. Both tables demonstrate clearly that the smallest prediction error was yielded by standard 1, the method of the relative deviate in terms of $x/\sigma$. The method is hardly new but is too often neglected. The closeness of correspondence is made conspicuous by insertion of the adjusted private school standard as a thin line in charts 1 and 2.

Weight: Since this fluctuated so much, we have been satisfied with plotting the points and setting up only one adjusted standard. This

43. Scammon, R. E., and Calkins, L. A.: Simple Empirical Formulae for Expressing the Lineal Growth of the Human Fetus, Proc. Soc. Exper. Biol. & Med. **20**:353, 1923.

was obtained by the method most successful with stature, namely, calculation of the relative deviate, $x/\sigma$. In the case of weights we took as best estimate the average of 2 close values at the ages 4 and 5 years, obtaining for J. G. 0.445 $\sigma$ and for H. C. C. 0.245 $\sigma$. The resulting errors were disappointingly large for both girls, 4.09 and 5.90 per cent, respectively.

Each girl's weight series illustrates two facts which we have often noticed before, facts always amazing and sometimes important, which are observed from the age of about 13 years up:

1. A girl's weight may diverge markedly from the most suitable standard, despite absence of disease.

2. A girl's weight may fluctuate markedly from month to month, despite absence of dieting.

Other Physical Traits: Seriatim studies of growth in characteristics other than height and weight are practically nonexistent. We have made for one of these 2 children such a series of anthropologic measurements, over a period of years, which will be worked up in the near future.

## SUMMARY

The first seriatim study of human growth was reported by the great naturalist Buffon in 1777. It was considered sufficiently important by Scammon to be reported at length in 1927. In all this century and a half this method of study has received only piecemeal attention. No wonder, considering the difficulty of securing the obvious desiderata:

1. Initiation of observations at birth, not merely at about the eighth year.

2. Repetition at least annually.

3. Extension until prime (adulthood), not merely until the age of about 16 years.

4. Recording of several characteristics, not merely height or weight.

5. Knowledge of the racial-economic background.

6. Knowledge of the health of the subject.

7. Knowledge of the age of puberty of the subject.

All these criteria were achieved for one of our subjects and most of them for the other.

Comparison was made with several standards which seemed suitable. The best of these for prophecy was the private school series adjusted by the individual's position relative to that of other girls in terms of the approved statistical unit of reference, the $x/\sigma$ scale.

APPENDIX A.—*Data on J. G.**

| Date | Age, Yr. | Net Height, Mm. | Net Weight Kg. | Other Data |
|---|---|---|---|---|
| Dec. 8, 1921 | 0.000 | 530 | 4.08 | |
| Feb. 1, 1922 | 0.151 | ..... | 5.10 | |
| March 1, 1922 | 0.228 | ..... | 5.75 | |
| April 1, 1922 | 0.313 | ..... | 6.41 | |
| May 1, 1922 | 0.395 | ..... | 7.54 | |
| June 1, 1922 | 0.480 | ..... | 8.22 | |
| July 1, 1922 | 0.562 | ..... | 8.85 | |
| Aug. 1, 1922 | 0.647 | ..... | 8.90 | |
| Sept. 1, 1922 | 0.732 | ..... | 9.30 | |
| Oct. 1, 1922 | 0.814 | ..... | 10.2 | |
| Nov. 1, 1922 | 0.899 | ..... | 10.9 | |
| Dec. 8, 1922 | 1.000 | ..... | 11.5 | |
| Feb. 15, 1923 | 1.189 | ..... | .... | Grip |
| June 1, 1923 | 1.480 | ..... | 12.3 | |
| Dec. 8, 1923 | 2.000 | 880 | 13.7 | |
| June 1, 1924 | 2.480 | ..... | 15.0 | |
| Nov. 15, 1924 | 2.937 | ..... | .... | Chickenpox |
| Dec. 1, 1924 | 2.981 | 985 | 15.0 | |
| June 1, 1925 | 3.480 | 1,017 | 16.7 | |
| Dec. 1, 1925 | 3.981 | 1,044 | 18.0 | |
| April 23, 1926 | 4.373 | ..... | .... | Tonsillectomy |
| June 1, 1926 | 4.480 | 1,082 | 19.5 | |
| Dec. 5, 1926 | 4.982 | 1,130 | 20.9 | |
| June 1, 1927 | 5.480 | 1,164 | 21.5 | |
| Dec. 1, 1927 | 5.981 | 1,208 | 23.6 | |
| June 1, 1928 | 6.480 | 1,254 | 24.5 | |
| Dec. 8, 1928 | 7.000 | 1,273 | 27.2 | |
| June 1, 1929 | 7.480 | 1,300 | 28.6 | |
| Dec. 1, 1929 | 7.961 | 1,333 | 29.0 | |
| June 1, 1930 | 8.480 | 1,369 | 29.9 | |
| Dec. 8, 1930 | 9.000 | 1,400 | 31.3 | |
| June 1, 1931 | 9.480 | 1,431 | 33.1 | |
| Sept. 8, 1931 | 9.751 | ..... | .... | Basal metabolic rate —13%; pulse rate 80, 80 |
| Dec. 1, 1931 | 9.981 | 1,462 | 33.6 | |
| June 1, 1932 | 10.480 | 1,497 | 37.6 | |
| Dec. 8, 1932 | 11.000 | 1,537 | 39.0 | |
| June 1, 1933 | 11.480 | 1,567 | 42.6 | |
| Nov. 22, 1933 | 11.956 | ..... | .... | Menarche |
| Dec. 1, 1933 | 11.981 | 1,598 | 46.3 | |
| June 1, 1934 | 12.480 | 1,615 | 47.2 | |
| Dec. 8, 1934 | 13.000 | 1,633 | 47.8 | |
| June 1, 1935 | 13.480 | 1,640 | 52.2 | Started administration of 0.015 Gm. (¼ grain) thyroid (Armour and Co.) |
| Dec. 1, 1935 | 14.041 | 1,643 | 56.1 | |
| Jan. 10, 1936 | 14.091 | ..... | .... | Dose of thyroid changed to 0.06 Gm. (1 grain), administered to time of report |
| June 9, 1936 | 14.502 | 1,654 | 61.2 | |
| June 26, 1936 | 14.548 | ..... | .... | Basal metabolic rate —16%; pulse rate 70, 70 |
| Dec. 8, 1936 | 15.000 | 1,666 | 61.2 | |
| June 1, 1937 | 15.480 | 1,668 | 61.2 | |
| Aug. 21, 1937 | 15.702 | ..... | .... | Basal metabolic rate —21%; pulse rate 76, 76 |
| Dec. 8, 1937 | 16.000 | 1,671 | 61.2 | |
| June 1, 1938 | 16.480 | 1,672 | 61.2 | |
| Sept. 2, 1938 | 16.734 | ..... | .... | Basal metabolic rate —14%; pulse rate 72, 72 |
| Dec. 8, 1938 | 17.000 | 1,673 | 59.9 | |
| April 7, 1939 | 17.329 | ..... | .... | Basal metabolic rate +1%; pulse rate 68, 68 |

* Age is calculated with the aid of a table such as that of Toops [18] or of Pearl and Miner.[19]

## APPENDIX B.—*Data on H. C. C.**

| Date | Age, Yr. | Net Height, Mm. | Net Weight, Kg. | Other Data |
|---|---|---|---|---|
| March 20, 1921 | 0.000 | 470 | 3.63 | |
| April 20, 1921 | 0.085 | 540 | 4.16 | |
| May 15, 1921 | 0.167 | 572 | 4.73 | |
| June 19, 1921 | 0.249 | 606 | 5.48 | |
| July 17, 1921 | 0.326 | 632 | 6.33 | |
| Aug. 30, 1921 | 0.446 | 662 | 7.18 | |
| Sept. 20, 1921 | 0.504 | 682 | 7.42 | |
| Oct. 23, 1921 | 0.594 | 697 | 8.26 | |
| Nov. 27, 1921 | 0.690 | 711 | 8.57 | |
| Jan. 1, 1922 | 0.786 | 724 | 8.98 | |
| Jan. 29, 1922 | 0.863 | 730 | 8.95 | |
| Feb. 19, 1922 | 0.920 | 733 | 9.15 | |
| March 20, 1922 | 1.000 | 749 | 9.45 | |
| Sept. 17, 1922 | 1.496 | ... | 10.71 | |
| Oct. 29, 1922 | 1.600 | ... | ..... | Tonsillitis |
| March 20, 1923 | 2.000 | 851 | 12.28 | |
| Sept. 12, 1923 | 2.482 | 899 | 13.78 | |
| March 20, 1924 | 3.000 | 943 | 14.23 | |
| Sept. 25, 1924 | 3.520 | 984 | 15.99 | |
| March 20, 1925 | 4.000 | 1,026 | 17.69 | |
| Aug. 3, 1925 | 4.372 | 1,067 | 18.46 | |
| March 20, 1926 | 5.000 | 1,105 | 20.34 | |
| Dec. 28, 1926 | 5.775 | 1,156 | 21.89 | |
| March 20, 1927 | 6.000 | 1,188 | 22.68 | |
| Oct. 5, 1927 | 6.545 | 1,226 | 26.65 | |
| March 20, 1928 | 7.000 | 1,251 | 28.69 | |
| Oct. 15, 1928 | 7.572 | 1,292 | 26.65 | |
| March 20, 1929 | 8.000 | 1,317 | 30.39 | |
| Sept. 17, 1929 | 8.496 | 1,340 | 30.39 | |
| March 20, 1930 | 9.000 | 1,368 | 35.38 | |
| Sept. 20, 1930 | 9.504 | 1,388 | 35.95 | |
| March 20, 1931 | 10.000 | 1,407 | 35.61 | |
| April 15, 1931 | 10.100 | ..... | ..... | Measles |
| Sept. 21, 1931 | 10.507 | 1,438 | 34.23 | |
| Feb. 26, 1932 | 10.989 | 1,454 | 37.65 | |
| Sept. 20, 1932 | 11.504 | 1,486 | 37.42 | |
| March 25, 1933 | 12.013 | 1,509 | 42.18 | |
| Sept. 21, 1933 | 12.507 | 1,530 | 45.81 | |
| March 20, 1934 | 13.000 | 1,568 | 48.76 | |
| Sept. 21, 1934 | 13.507 | 1,597 | 52.16 | |
| March 20, 1935 | 14.000 | 1,627 | 56.22 | |
| May 15, 1935 | 14.200 | ..... | ..... | Menarche |
| Nov. 23, 1935 | 14.679 | 1,651 | 57.72 | |
| Feb. 7, 1936 | 14.900 | ..... | ..... | Pneumonia |
| March 20, 1936 | 15.000 | 1,664 | 57.61 | |
| Sept. 20, 1936 | 15.504 | 1,688 | 59.87 | |
| March 20, 1937 | 16.000 | 1,695 | 63.50 | |
| Sept. 20, 1937 | 16.504 | 1,695 | 62.14 | |
| March 20, 1938 | 17.000 | 1,695 | 62.60 | |
| Sept. 20, 1938 | 17.504 | 1,695 | 61.69 | |
| March 20, 1939 | 18.000 | ..... | 59.42 | |
| June 20, 1939 | 18.252 | 1,702 | 60.30 | |

* See footnote, appendix A.

# HUMAN HEMOLYTIC STREPTOCOCCI FROM DISEASES OF CHILDREN

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Lancefield [1] has demonstrated that hemolytic streptococci can be divided into distinct groups by means of a precipitin test which identifies specific carbohydrates. Strains from human disease were observed to fall into one group, which she designated as group A.[2] Her groups B, C, D, E, F and G consisted of animal strains and human saprophytes.[3]

With the wider employment of the Lancefield group precipitin test, some exceptions have appeared. Hemolytic streptococci of groups other than A have been found in association with infection, even fatal infection, in man. Hare [4] and Fry [5] isolated group B hemolytic streptococci from a total of 11 patients with puerperal sepsis; in 4 of the 5 patients who died of the infection the organisms were recovered from the blood. Hare [4] found that Griffith's [6] type 7 hemolytic streptococcus, recovered from human erysipelas, fell into Lancefield's group C. Plummer [7] classified 2 strains from puerperal fever and 3 from erysipelas as group C.

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From the Department of Pediatrics, Yale University School of Medicine, and the Pediatric Service of the New Haven Hospital and Dispensary.

1. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933.

2. By means of another precipitin test previously described by Lancefield in 1928 (Lancefield, R. C.: The Antigenic Complex of Streptococcus Hemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Hemolyticus, J. Exper. Med. **47**:91, 1928), which detects type specific protein, or by the slide agglutination method of Griffith (Griffith, F.: The Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542, 1934), group A may be subdivided into over 20 types.

3. Using the Lancefield method, Hare (Hare, R.: The Classification of Hemolytic Streptococci from the Nose and Throat of Normal Human Beings by Means of Precipitin and Biochemical Tests, J. Path. & Bact. **41**:499, 1935) has added 2 new groups, H and K.

4. Hare, R., cited in footnote 3.

5. Fry, R.: Fatal Infections by Hemolytic Streptococcus Group B, Lancet **1**:199, 1938.

6. Griffith, F., cited in footnote 2.

7. Plummer, H.: A Serological Study of Hemolytic Streptococci, J. Bact. **30**:5, 1935.

Of strains from fatal human diseases, Coffey [8] reported 2 to be group B and 3 to be group C or G. Morales-Otero and Pomales-Lebron [9] recovered a group G organism from the blood of a patient with sepsis. Long and associates [10] isolated members of group F in pure culture from acute sinusitis and from a deep abscess of the chest. Coffey [8] recovered a group F strain in pure culture from pleural fluid.

Except for these restrictions Lancefield's work has been generally corroborated, and the close relationship of group A hemolytic streptococci to human disease has been confirmed in many laboratories.

Heretofore, the results of the Lancefield method of classification have not been correlated with the age of the patients who furnished the material for the cultures. My associates and I believed it would be of interest to collect data on the relative importance of these various serologic groups in the streptococcic infections of infants and children. Since children have a high mortality from hemolytic streptococcic infections as compared with adults, there was reason to suspect that those groups, other than the human pathogenic A, which can cause human disease might commonly be found to be a cause of infection. Therefore, we studied the clinical material available at the New Haven Hospital. It has a fairly active pediatric service of 60 beds, with between 700 and 800 patients admitted yearly. Infants and children having all types of disease are accepted, and patients with streptococcic disease furnish about one fourth of the total number admitted to the pediatric service. It was believed that a year or more of study of the hemolytic streptococci recovered from these infants and children with various types of streptococcic infection should establish the importance of the different serologic groups in pediatric practice.

## METHOD OF STUDY

For sixteen months (Oct. 1, 1936 to Feb. 1, 1938), all strains of hemolytic streptococci which came to the laboratory were grouped by the Lancefield method. The majority of strains were obtained from patients in the pediatric wards of the New Haven Hospital. Additional strains were obtained whenever possible from infants and children in the surgical wards, in the pediatric outpatient clinic, in nearby institutions and in

8. Coffey, J.: Tentative Methods for the Isolation and Identification of Hemolytic Streptococci, Am. J. Pub. Health (supp.) **27**:135, 1937; Evaluation of the Group-Precipitin Test in the Identification of Hemolytic Streptococci Pathogenic for Man, ibid. **28**:104, 1938.

9. Morales-Otero, P., and Pomales-Lebron, A.: Grouping of Hemolytic Streptococci Isolated in Puerto Rico, Proc. Soc. Exper. Biol. & Med. **34**:105, 1936.

10. Long, P.; Bliss, E., and Walcott, C.: Studies on Minute Hemolytic Streptococci: II. The Distribution of Minute Hemolytic Streptococci in Normal and Diseased Human Beings, J. Exper. Med. **60**:633, 1934.

private homes. All of the persons were from New Haven and its vicinity. In all instances there was evidence, either clinical or bacteriologic, that the infection was of hemolytic streptococcic origin.

*Isolation of Strains.*—A fresh beef heart infusion with 1 per cent neopeptone was the basic medium used. The stock infusion was prepared from hearts obtained the day of slaughtering. Blood agar plates containing 5 per cent of rabbit blood were made daily. For blood broth tubes, 1 per cent of rabbit blood was used. Cultures of material from the nose and the throat, of blood and of material from purulent lesions (spinal fluid, pleural fluid, aural discharge and mastoid pus) were made at the time of the patient's admission and subsequently when indicated. These bacteriologic studies are part of the routine examination of patients at the New Haven Hospital. Swabbings from the nose and throat were streaked separately on rabbit's blood agar plates and incubated aerobically at 37.5 C. The cotton swabs from both the nose and the throat were then agitated in about 1 cc. of broth, without added rabbit blood, and this was injected intraperitoneally into a white mouse. The blood agar plates were read when bacterial growth seemed optimal (generally after eighteen to twenty-four hours' incubation). An autopsy was performed on the mouse at the time of its death, or it was killed when sick and an autopsy performed. The blood of its heart and the peritoneal exudate were cultured on blood agar plates. In case of survival, the mouse was killed on the fourth day after inoculation and examined bacteriologically in the same manner.

Blood cultures were made by adding 5 to 7 cc. of the patient's blood to 50 cc. of broth, and by mixing 2 cc. of citrated blood of the patient with 15 cc. of infusion agar to form a pour plate. Broth cultures were read as negative if a smear of the broth after five days of incubation showed no organisms. Pour plates were discarded if no colonies were visible at the end of forty-eight hours.

Purulent exudates were inoculated into the blood broth, streaked on a blood agar plate and injected into a mouse.

Material from patients in the clinic or in the wards of the hospital was cultured promptly. With patients seen outside of the hospital, mediums were inoculated at the time and incubated as soon as possible, usually within an hour.

Positive broth cultures from sources already named were subcultured on blood agar plates. Portions of colonies on the plates which resembled those of the hemolytic streptococcus were smeared, stained and examined microscopically. If gram-positive cocci were found, the remainder of the colony was isolated in broth for further studies.

*Bile Solubility Test.*—Eight-tenths cubic centimeter of an eighteen hour broth culture of the organism plus 0.2 cc. of 10 per cent ox bile was placed in an agglutination tube and incubated in a water bath at 37.5 C. The test was read as negative if there was no clearing at the end of two hours.

*Hemolysin Test.*—Five-tenths cubic centimeter of an eighteen hour broth culture was added to 0.5 cc. of a 5 per cent suspension of fresh washed rabbit erythrocytes in physiologic solution of sodium chloride. Final readings were made after two hours' incubation in a water bath.

*Serologic Grouping.*—Immune Serums: The method used was essentially that of Lancefield. Albino rabbits weighing from 2.5 to 3 Kg. were immunized by intravenous inoculation with hemolytic streptococci known to belong in groups A, B, C, F, G and H. Heat-killed organisms were used for the production of the group A antiserum. For the other groups cultures treated with formaldehyde were employed in producing the antiserums. Such antiserums were satisfactory in respect to potency and group specificity.

*Extracts.*—An extract of each strain to be grouped was made by treating the bacterial sediment from 30 cc. of an eighteen hour broth culture with hot hydrochloric acid. The group-specific carbohydrate (C substance) was liberated by this means.

*Precipitin Test.*—The clear extract of each strain was placed in three small glass tubes, 100 by 8 mm., 0.4, 0.2 and 0.1 cc. of the extract being used. Volumes were made up to 0.4 cc. with physiologic solution of sodium chloride. Two-tenths cubic centimeter of group-specific rabbit antiserum was layered in each tube. A control tube of diluent and antiserum alone was included. The tubes were allowed to stand at room temperature for about twenty minutes, and ring formation if present was noted. The tubes were then shaken, incubated in a water bath at 37.5 C. for two hours and placed in the ice box overnight. Final readings were made the following morning. The extract from each strain was tested against antiserum for each of the six groups.

TABLE 1.—*Age Distribution of Patients with Hemolytic Streptococcic Infection .*

| Total Number of Patients | Infants (Less than 2 Yrs.) | Children (2-16 Yrs.) |
|---|---|---|
| 262 | 49 | 213 |

TABLE 2.—*Clinical Types of Streptococcic Infection and Sources of Strains of Hemolytic Streptococci* *

| Disease | Nose | Throat | (Mouse) | Ear | Blood | Mastoid | Abscess | Pleural Fluid |
|---|---|---|---|---|---|---|---|---|
| Scarlet fever.....(73) | 24 | 73 | 30 | 3 | 1 | .. | 5 | 4 |
| Tonsillitis.....(80) | 22 | 80 | 19 | 2 | .. | .. | 6 | .. |
| Pneumonia.....(9) | 4 | 6 | 4 | 1 | 2 | .. | .. | 9 |
| Mastoiditis.....(7) | .. | .. | .. | 1 | 2 | 3 | 1 | .. |
| Otitis media.....(36) | 10 | 20 | 7 | 40 | 1 | 2 | 2 | .. |
| Suppurative adenitis...(10) | 1 | 2 | .. | .. | .. | .. | 10 | .. |
| Sinusitis.....(1) | 1 | 1 | 1 | .. | .. | .. | .. | .. |

| | Nose | Throat | (Mouse) | Skin | Blood | Spinal Fluid | Abscess | Pericardial Fluid |
|---|---|---|---|---|---|---|---|---|
| Erysipelas.....(15) | 10 | 8 | 7 | 7 | 6 | .. | 7 | .. |
| Cellulitis.....(12) | 2 | 2 | 3 | .. | .. | .. | 12 | .. |
| Meningitis.....(2) | .. | .. | .. | .. | 2 | 2 | .. | . |
| Septicemia.....(6) | 2 | 5 | 3 | .. | 6 | 1 | 1 | .. |
| Pericarditis.....(1) | .. | .. | .. | .. | .. | .. | .. | 1 |
| (Nephritis)†.....(5) | 1 | 4 | 2 | .. | .. | .. | 2 | .. |
| (Rheumatic fever).....(5) | 1 | 5 | 2 | .. | .. | .. | .. | .. |

* Figures in parentheses represent the number of patients.
† Diseases in parentheses are sequelae to streptococcic infections.

## RESULTS

During the sixteen months of study, 509 strains of hemolytic streptococci from 262 patients with streptococcic disease were isolated and grouped by the Lancefield method. Of the patients, 49 were infants and 213 were children (table 1).

The clinical types of hemolytic streptococcic infection encountered and the sources of the strains studied are given in table 2. This table gives a general idea of the spread of hemolytic streptococci through the

body. This classification of streptococcic disease is not consistently clinical or anatomic, as it seems nearly impossible to divide in a uniform manner the many manifestations of infection by the hemolytic streptococcus. After several methods had been attempted, a classification based on our idea of current pediatric practice and on the presenting disease process was used.

In table 2 there appear all of the common types of disease which are generally regarded by clinicians as caused by hemolytic streptococci or as possible or probable sequelae to such infections (e. g., rheumatic fever and nephritis).

Strains from all available sources in a patient were isolated and studied separately, because if all the strains fell into one group this would furnish evidence of the etiologic relationship of the streptococci being

TABLE 3.—*Results of Lancefield Precipitin Test* *

| Disease | No. of Strains | Lancefield Group | | | | | |
|---|---|---|---|---|---|---|---|
| | | A | B | C | F | G | H |
| Scarlet fever.....(73) | 140 | 140 | — | — | — | — | — |
| Tonsillitis.....(80) | 129 | 129 | — | — | — | — | — |
| Pneumonia..... (9) | 26 | 26 | — | — | — | — | — |
| Mastoiditis..... (7) | 12 | 12 | — | — | — | — | — |
| Otitis media.....(36) | 82 | 82 | — | — | — | — | — |
| Suppurative adenitis.....(10) | 13 | 13 | — | — | — | — | — |
| Sinusitis..... (1) | 3 | 3 | — | — | — | — | — |
| Erysipelas.....(15) | 45 | 45 | — | — | — | — | — |
| Cellulitis.....(12) | 19 | 19 | — | — | — | — | — |
| Meningitis..... (2) | 4 | 4 | — | — | — | — | — |
| Septicemia..... (6) | 18 | 18 | — | — | — | — | — |
| Pericarditis..... (1) | 1 | 1 | — | — | — | — | — |
| (Nephritis)†..... (5) | 9 | 9 | — | — | — | — | — |
| (Rheumatic fever)..... (5) | 8 | 8 | — | — | — | — | — |

* Figures in parentheses represent the number of cases.
† Diseases in parentheses are sequelae to streptococcic infections.

examined. In the large majority of instances, strains from two or more sources were obtainable from patients in the pediatric service and from patients seen outside the hospital. From patients in other services of the hospital, sometimes only one strain was isolated, as it was not always possible to obtain culture material from all suspected sources of the organism. When only one strain could be obtained, two colonies of hemolytic streptococci as dissimilar as possible in appearance were picked from a blood agar plate and studied separately. Strains recovered from mice inoculated with infected material were also grouped, as members of groups B and C are generally more highly virulent for mice than organisms of group A and their presence in the original inoculum, even in relatively small numbers, might be demonstrated by this means. However, none but group A streptococci were recovered this way.

All of the 509 strains of hemolytic streptococci from these 262 patients with various types or possible sequelae of streptococcic disease fell into

group A (table 3). The results of the precipitin test were in all instances clearcut, no difficulty with cross reactions being encountered. There were no strains which could not be grouped, and in no case was there encountered clinical hemolytic streptococcic infection from which the organism could not be recovered. All the strains produced a soluble hemolysin and were insoluble in bile.

As part of another study, strains from various sources were collected, and hemolytic streptococci of groups B, C, F and G were identified. This proved that our diagnostic serums were adequate.

## COMMENT

The Lancefield group precipitin test gave consistent results and seems well adapted for epidemiologic use. The results suggest that infants and children are no more, and may be less, susceptible than adults to infection by hemolytic streptococci of groups other than A. It seems significant to us that during a period of over a year all the strains of hemolytic streptococci from clinical streptococcic infections and their possible sequelae should belong in the one group, group A. Thus, 509 strains of group A hemolytic streptococci were consecutively obtained from 262 pediatric patients.

## CONCLUSION

Infants and children are no more susceptible than adults to infection by hemolytic streptococci of groups other than A.

NOTE.—This study is being continued and is now in its fourth year. The only exception to date is the isolation this fall of a group F hemolytic streptococcus from the blood of a 7 year old child with a nonfatal septicemia.

Dr. Rebecca C. Lancefield, of the Hospital of the Rockefeller Institute for Medical Research, furnished me with hemolytic streptococci of known groups for producing group-specific rabbit antiserums.

# FACTORS INFLUENCING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

## III. PUBERTY IN THE NORMAL GIRL AND IN THE GIRL WITH THE MINIMAL REINFECTION TYPE OF TUBERCULOSIS

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DETROIT

The well authenticated observation of the sharp increase in the adult form of tuberculosis in the girl at puberty, with the similar incidence in the boy maturing a few years later, has constantly been related in the minds of workers in that field to the possibility that an alteration in metabolism at this period might play a role in the activation of a hitherto latent lesion, and it has made desirable more information on the nutritional requirement in this seemingly critical age period. It was my own confirmation of this phenomenon in the course of a ten year follow-up of tuberculin reactors to detect the onset of the adult type lesion that led me to this study. Nineteen of the 29 patients with the adult type of tuberculosis detected in this survey were girls, and of these, 16 had contracted it between the ages of 11 and 17.

While currently less importance is attached to the endogenous manner of contracting the reinfection type of tuberculosis [1] than to the exogenous manner, I feel that definite evidence exists of the occurrence of the former,[2] and in discussing the situation as it exists at puberty, the League of Nations Committee stressed its feeling that the problem is a nutritional one.[3]

It was a thesis which Brailsford Robertson [4] developed at length that growth in man consisted of alternating rapid and slow periods, the

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Read at the Annual Meeting of the American Pediatric Society, Skytop, Pa., April 28, 1939.

One of a series of metabolic investigations in connection with the study of tuberculosis in childhood being conducted for the Society of St. Vincent de Paul under the joint auspices of the Henry Ford Hospital and the Children's Fund of Michigan.

1. Pope, A. S.: Application of Our Knowledge of Tuberculosis Through Case Finding, Nat. Tuberc. A. Tr. **31**:317, 1935.

2. Johnston, J. A.: Evolution of the Adult Type of Tuberculosis from the Childhood Type: Evidence in Favor of Endogenous Reinfection, J. Pediat. **9**: 350 (Sept.) 1936.

3. The Problem of Nutrition: I. Interim Report of the Mixed Committee on the Problem of Nutrition of the League of Nations, New York, Columbia University Press, 1936, pp. 48-49.

4. Robertson, T. B.: The Chemical Basis of Growth and Senescence, Philadelphia, J. B. Lippincott Company, 1923.

curve revealing distinct waves or large oscillations which might roughly be likened to three S-shaped curves one on another. The first of these, he felt, terminated at the end of the first year, after which a resting period was succeeded by a fairly rapid period of growth in the third, fourth and fifth years. Another pause succeeded this period of growth, to be followed by the energetic growth which accompanies adolescence. The transition from one cycle to another, he pointed out, involved profound chemical and metabolic changes, which might be fraught with considerable danger to the growing child.

That the growth in the pubertal period is a reflection of physiologic age rather than of chronologic age is evident from the studies of Boas [5] and of Shuttleworth,[6] which brought out strikingly that the curves of the rates of growth of girls whose menarche showed a range of incidence of five years could be superimposed if chronologic age was ignored and the curves were plotted in terms of years preceding and following the onset of the menses. Too much stress, however, should not be placed on the incident of the first menstrual period itself as exactly determining the point of sexual maturity. In studying the curves to be presented in this study cyclic variations in retention will be evident for months preceding the menarche and following it.

The observation of the growth process over any length of time in human beings has necessarily been limited to anthropometric measurements, and yet over a long period a gain in weight can be observed as a result of increments of water and fat without concurrent retention of those substances which enter into the structure of muscle and bone, and the inadequacy of a diet can be obscured if weight is used as a measure of dietary need. The interesting phenomenon of a failure to lose weight on an amount of food on which loss would normally be expected, particularly if the food contains too little nitrogen, is apparently the result of a fall in basal metabolism, carrying with it presumably the ill effects inherent in that condition itself.[7] Conversely, it will be shown in this study that high retentions of calcium and nitrogen are possible over the prolonged periods during which weight is being lost (charts 4 and 6).

An adequate literature on the basal metabolism of girls as affected by puberty was reviewed by Topper and Mulier,[8] whose own data con-

5. Boas, F.: Studies in Growth, Human Biol. **4**:307 (Sept.) 1932.

6. Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, National Research Council, 1937, vol. 2, no. 5.

7. Johnston, J. A., and Maroney, J. W.: Relationship of Basal Metabolism to Dietary Intake, Am. J. Dis. Child. **51**:1039 (May) 1936.

8. Topper, A., and Mulier, H.: Basal Metabolism of Normal Children: Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

firm a premenarcheal rise in metabolic rate and a postmenarcheal fall. I have not found a similar work in which balances were recorded, although a considerable body of work recording retentions sporadically throughout this period was reviewed by Wang and his associates [9] and by Leitch.[10] The magnitude of the retentions which I have recorded corresponds roughly with those recorded by these authors, but the influence of the actual incident of the first menstrual period is not, to my knowledge, available.

## PLAN AND METHODS OF STUDY

The first 3 children whose cases are to be reported were convalescent from a childhood type of tuberculosis for which they had been hospitalized in the Northville Sanatorium under Dr. Willis, who selected them for this study on the basis of the appearance of secondary sex characteristics. Their parenchymatous lesions had absorbed, and they would normally have gone on a regimen of exercise or have been discharged to their own homes, if these were adequate.

While the disadvantage of studying convalescents is obvious, it is to a large extent, I feel, offset by the fact that for a long time prior to the study they had been on known diets, and judged by weight most of them were well nourished. During the balance studies in the hospital, the children attended two sessions of school daily for two hours in the morning and two in the afternoon, had rest periods of an hour each morning and afternoon and worked in the garden in the summer months.

The second group of 3 girls had been hospitalized with minimal adult type lesions sufficiently slight so that collapse therapy had not seemed indicated. All were afebrile and asymtomatic. In the course of the study, however, an extension of the process in Josephine L. required pneumothorax.

Standard diets 1-6 were prepared from staple foods, changing each day for six days in rotation, and were proportioned calorically 15 per cent from protein, 35 per cent from fat and 50 per cent from carbohydrate.[11] At the beginning of the study, attempt was made to ascertain the total amount the child would take with appetite and without refusal and to keep this amount given to the child constant throughout the study. Refusals were analyzed. At the end of a six day period, an analysis of the diet was carried out, one sixth of the content of each of the six diets being used. These methods have already been described

9. Wang, C. C.; Kaucher, M., and Wing, M.: Metabolism of Adolescent Girls: Mineral Metabolism, Am. J. Dis. Child. **52**:41 (July) 1936.

10. Leitch, I.: Determination of Calcium Requirements of Man, Nutrition Abstr. & Rev. **6**:553 (Jan.) 1937.

11. Maroney, J. W., and Johnston, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from Four to Fourteen Years Old, Am. J. Dis. Child. **54**:29 (July) 1937.

TABLE 1.—*Data for Velma G.*

| 6 Day Periods | 1937-1938 Dates* | Nitrogen, Gm. | | | | Retention, Mg. per Kg. | Calcium, Gm. | | | | Retention, Mg. per Kg. | Basal Metabolic Rate, Percentage | Respiratory Quotient | Calories per Square Meter per Hour | Basal Calories | Weight, Pounds | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Food Intake | Urine | Stool | Balance | | Food Intake | Urine | Stool | Balance | | | | | | | |
| 1 | 10/15-19 | 12.47 | 6.80 | 1.15 | +4.52 | .... | 1.245 | 0.022 | 0.728 | +0.495 | .... | — 5 | 0.80 | 43.5 | 1,200 | 78½ | |
| | | | | | | | | | | | | — 8 | 0.82 | 42.0 | 1,149 | 79 | |
| 2 | 10/20-25 | 12.47 | 8.30 | 1.01 | +3.16 | .... | 1.245 | 0.018 | 0.630 | +0.597 | .... | — 7 | 0.81 | 42.6 | 1,175 | 79 | |
| 3 | 10/26-31 | 12.47 | 8.57 | 1.14 | +2.76 | .... | 1.245 | 0.021 | 1.045 | +0.179 | .... | — 6 | 0.83 | 42.9 | 1,195 | 79 | |
| | | | | | | | | | | | | — 5 | 0.82 | 43.7 | 1,216 | 79 | |
| 4 | 11/ 1- 6 | 12.47 | 8.66 | 1.04 | +2.77 | .... | 1.245 | 0.009 | 0.422 | +0.813 | .... | — 5 | 0.76 | 43.9 | 1,222 | 79½ | |
| | | | | | | | | | | | | — 9 | 0.81 | 41.4 | 1,142 | 79¼ | |
| 5 | 11/ 7-12 | 12.47 | 6.89 | 1.15 | +4.43 | .... | 1.245 | 0.028 | 0.477 | +0.740 | .... | — 8 | 0.81 | 41.8 | 1,153 | 79¼ | |
| | | | | | | | | | | | | — 8 | 0.82 | 42.1 | 1,172 | 79½ | |
| 6 | 11/13-18 | 12.47 | 6.71 | 1.15 | +4.61 | .... | 1.245 | 0.017 | 0.581 | +0.647 | .... | — 6 | 0.86 | 43.3 | 1,215 | 80½ | |
| 7 | 11/19-24 | 12.47 | 9.42 | 1.19 | +1.86 | .... | 1.245 | 0.018 | 0.726 | +0.501 | .... | — 1 | 0.84 | 45.3 | 1,261 | 79 | |
| | | | | | | | | | | | | —11 | 0.78 | 40.4 | 1,134 | 80¼ | |
| 8 | 11/25-30 | 12.47 | 8.67 | 1.19 | +2.61 | .... | 1.245 | 0.028 | 0.802 | +0.415 | .... | + 4 | 0.82 | 47.5 | 1,333 | 80¾ | |
| | | | | | | | | | | | | — 8 | 0.78 | 41.9 | 1,176 | 80 | |
| 9 | 12/ 1- 6 | 12.48 | 9.51 | 1.22 | +1.75 | .... | 1.202 | 0.023 | 0.792 | +0.387 | .... | —12 | 0.77 | 40.3 | 1,131 | 80½ | |
| 10 | 12/ 7-12 | 12.48 | 9.17 | 1.23 | +2.08 | .... | 1.159 | 0.021 | 0.722 | +0.416 | .... | —13 | 0.86 | 39.9 | 1,120 | 80½ | |
| 11 | 12/13-18 | 12.48 | 10.30 | 1.33 | +0.85 | .... | 1.159 | 0.034 | 0.780 | +0.345 | .... | — 6 | 0.78 | 42.8 | 1,201 | 80 | |
| | | | | | | | | | | | | — 2 | 0.80 | 45.0 | 1,263 | 81 | |
| 12 | 12/19-24 | 12.39 | 9.34 | 1.02 | +2.03 | .... | 1.165 | 0.029 | 0.339 | +0.797 | .... | — 8 | 0.82 | 42.2 | 1,184 | 81 | |
| 13 | 12/25-30 | 12.29 | 9.59 | 1.08 | +1.62 | .... | 1.171 | 0.028 | 0.706 | +0.437 | .... | —11 | 0.78 | 40.8 | 1,155 | 81½ | |
| | | | | | | | | | | | | — 6 | 0.84 | 42.9 | 1,215 | 82 | Menarche |
| | Average..... | | | | +2.69 | 66.4 | ..... | ..... | ..... | +0.495 | 13.6 mg. | .... | .... | .... | ..... | 80 (36.4 Kg.) | |
| 14 | 12/31-1/5 | 12.29 | 11.04 | 1.16 | +0.09 | .... | 1.171 | 0.008 | 0.816 | +0.347 | .... | — 8 | 0.84 | 41.8 | 1,183 | 81½ | |
| 15 | 1/ 6-11 | 12.29 | 9.85 | 1.13 | +1.31 | .... | 1.171 | 0.017 | 0.780 | +0.394 | .... | —13 | 0.86 | 39.6 | 1,121 | 82 | |
| 16 | 1/12-17 | 12.29 | 9.54 | 1.00 | +1.75 | .... | 1.171 | 0.022 | 0.635 | +0.514 | .... | —14 | 0.82 | 39.1 | 1,107 | 82½ | |
| 17 | 1/18-23 | 12.33 | 10.00 | 1.09 | +1.24 | .... | 1.188 | 0.025 | 0.726 | +0.437 | .... | —10 | 0.85 | 41.0 | 1,161 | 82½ | |
| | | | | | | | | | | | | — 4 | 0.86 | 43.6 | 1,234 | 83½ | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 1/24-29 | 12.36 | 9.55 | 0.87 | +1.94 | .... | 1.205 | 0.039 | 0.645 | +0.521 | .... | —10 | 0.82 | 41.3 | 1,169 | 82¾ | |
| | | | | | | | | | | | | —11 | 0.81 | 40.8 | 1,164 | 83½ | |
| 19 | 1/30-2/4 | 12.36 | 9.78 | 1.19 | +1.39 | .... | 1.205 | 0.036 | 0.949 | +0.220 | .... | —11 | 0.83 | 40.9 | 1,177 | 84½ | |
| | | | | | | | | | | | | —10 | 0.83 | 40.8 | 1,175 | 84 | |
| 20 | 2/ 5-10 | 12.36 | 9.39 | 0.97 | +2.00 | .... | 1.205 | 0.029 | 0.860 | +0.286 | .... | — 9 | 0.83 | 41.6 | 1,178 | 82 | Menses |
| 21 | 2/11-16 | 12.36 | 9.71 | 1.07 | +1.58 | .... | 1.205 | 0.028 | 1.072 | +0.105 | .... | —10 | 0.83 | 41.0 | 1,180 | 84½ | |
| | | | | | | | | | | | | — 6 | 0.82 | 43.2 | 1,233 | 83½ | |
| 22 | 2/17-22 | 12.40 | 10.23 | 1.09 | +1.08 | .... | 1.187 | 0.009 | 0.717 | +0.461 | .... | —12 | 0.82 | 40.2 | 1,157 | 84 | |
| | | | | | | | | | | | | — 9 | 0.75 | 41.7 | 1,220 | 85½ | |
| 23 | 2/23-28 | 12.49 | 8.70 | 1.04 | +2.75 | .... | 1.190 | 0.002 | 0.958 | +0.230 | .... | — 6 | 0.76 | 43.2 | 1,244 | 85½ | |
| 24 | 3/ 1- 6 | 12.39 | 9.15 | 1.04 | +2.20 | .... | 1.220 | 0.011 | 0.894 | +0.315 | .... | — 5 | 0.85 | 43.2 | 1,247 | 85¾ | |
| 25 | 3/ 7-12 | 12.33 | 8.94 | 1.31 | +2.08 | .... | 1.250 | 0.021 | 1.033 | +0.196 | .... | —15 | 0.79 | 38.5 | 1,127 | 86½ | |
| | | | | | | | | | | | | — 8 | 0.77 | 43.3 | 1,213 | 87 | |
| 26 | 3/13-18 | 12.33 | 9.35 | 0.89 | +2.07 | .... | 1.250 | 0.041 | 0.598 | +0.611 | | — 2 | 0.76 | 44.0 | 1,127 | 87½ | |
| | | | | | | | | | | | .... | — 4 | 0.81 | 43.8 | 1,213 | 87 | |
| | | | | | | | | | | | | — 7 | 0.83 | 42.7 | 1,253 | 87¾ | |
| 27 | 3/19-24 | 12.19 | 9.32 | 1.26 | +1.61 | .... | 1.190 | 0.018 | 0.930 | +0.242 | .... | — 7 | 0.80 | 42.4 | 1,259 | 90 | |
| 28 | 3/25-30 | 12.19 | 9.57 | 1.28 | +1.34 | .... | 1.190 | 0.002 | 0.718 | +0.470 | .... | — 6 | 0.80 | 43.0 | 1,248 | 88¾ | |
| | | | | | | | | | | | | —12 | 0.78 | 40.4 | 1,212 | 87¾ | |
| 29 | 3/31-4/5 | 12.43 | 9.56 | 1.27 | +1.60 | .... | 1.160 | 0.001 | 0.750 | +0.409 | .... | — 4 | 0.88 | 44.0 | 1,288 | 88½ | |
| 30 | 4/ 6-11 | 12.07 | 10.06 | 1.22 | +1.39 | .... | 1.130 | 0.005 | 0.734 | +0.392 | .... | — 7 | 0.87 | 42.4 | 1,279 | 89 | |
| 31 | 4/12-17 | 12.49 | 10.75 | 1.15 | +0.59 | .... | 1.130 | 0.002 | 0.778 | +0.350 | .... | —11 | 0.87 | 40.8 | 1,203 | 88¾ | |
| | | | | | | | | | | | | — 9 | 0.82 | 42.1 | 1,251 | 88 | |
| 32 | 4/18-23 | 12.31 | 9.87 | 1.27 | +1.17 | .... | 1.130 | 0.008 | 0.773 | +0.354 | .... | ± 0 | 0.81 | 45.6 | 1,335 | 87½ | |
| | | | | | | | | | | | | — 6 | 0.81 | 42.9 | 1,266 | 89¼ | |
| 33 | 4/24-29 | 12.31 | 10.46 | 1.26 | +0.59 | .... | 1.200 | 0.006 | 0.604 | +0.560 | .... | — 8 | 0.79 | 41.9 | 1,203 | 88 | |
| 34 | 4/30-5/5 | 12.63 | 10.02 | 1.25 | +1.36 | .... | 1.185 | 0.012 | 0.866 | +0.307 | .... | —12 | 0.88 | 40.0 | 1,171 | 88 | Menses |
| 35 | 5/ 6-11 | 12.47 | 10.76 | 1.01 | +0.70 | .... | 1.140 | 0.010 | 0.675 | +0.455 | .... | —16 | 0.90 | 37.9 | 1,111 | 87 | |
| 36 | 5/12-17 | 12.27 | 10.41 | 1.08 | +1.86 | .... | 1.155 | 0.009 | 0.796 | +0.350 | .... | —13 | 0.85 | 39.3 | 1,150 | 88 | |
| 37 | 5/18-23 | 12.53 | 8.76 | 0.98 | +2.79 | .... | 1.200 | 0.011 | 0.530 | +0.659 | | | | | | | |
| 38 | 5/24-29 | 12.53 | 8.29 | 0.93 | +3.31 | .... | 1.200 | 0.004 | 0.641 | +0.555 | .... | —14 | 0.73 | 39.5 | 1,166 | 88¾ | |
| | Average..... | | | | +1.57 | 40.3 mg. | ..... | ..... | ..... | +0.387 | 9.9 mg. | .... | .... | .... | ..... | 86 (38.9 Kg.) | |

* Five day period.

in previously published articles.[12] For the 3 children studied who had minimal adult type tuberculosis and for whom only the nitrogen balance was determined, the diets were not analyzed regularly each week but the intake was calculated from an analysis of fifty sample meals. With a varied intake of meat and vegetables, it was found that this dietary analysis exceeded that calculated from food tables by 11.75 per cent. The standards used were those of Boothby and Sandiford, but in the charting total calories per twenty-four hours were used so that the change is absolute rather than relative.[12a]

## FINDINGS FOR NORMAL CHILDREN

CASE 1.— V. G. (table 1, charts 1 and 2), a Negro girl born on Sept. 7, 1928, was found to have a first infection type of tuberculosis in July 1936, for which she was hospitalized in a sanatorium from October 1936 to October 1937. Roentgen examination had shown a parenchymatous shadow at the base of the lung, which cleared five months before her discharge. She had been taking graded exercise from May to October 1937. On admission to the sanatorium she had been slightly under average weight, but during her year's stay she had gained 18 pounds (8.2 Kg.), and on discharge she was 12 pounds (5.4 Kg.) above the estimated weight for her age and height in the Baldwin-Wood tables. On her transfer to the Henry Ford Hospital from the sanatorium in October 1937, roentgen examination showed that the lung was clear, and no abnormality was found except a questionable mild chronic tonsillitis. Roentgenograms made of the wrist showed a normal bone age. Evidence of secondary sex characteristics, enlarged breasts and pubic hair, were pronounced. Balance studies began October 15, 1937 and were charted in thirty-eight periods of six days each, in the thirteenth of which the menarche occurred.

The basal metabolism for twenty-four hours showed a range between 1,075 calories (basal metabolic rate of —15 per cent) and 1,334 calories (basal metabolic rate of +4 per cent), the high figure obtaining just before the menarche and the low shortly after. There was a direct parallelism between nitrogen and calcium retentions and metabolic rate, high retentions accompanying high rates and low retentions low rates.

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12. Johnston, J. A., and Maroney, J. W.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: (*a*) I. Effect of Thyroid on Nitrogen Retention, Am. J. Dis. Child. **58**:965 (Nov.) 1939; (*b*) II. Effect of Thyroid on Calcium Retention, ibid. **58**:1186 (Dec.) 1939.

12a. In the charts, within parentheses, and in the text, the metabolic rates are calculated from the surface area standards of Boothby and Sandiford. Since there is some question as to the validity of this type of standard in the growing child, calculations were also made from the height standards suggested by Talbot and his associates, and the comparisons of the extreme points in the ranges of the six subjects studied follow: Velma G., —15 to +4 Boothby surface area = ±0 to +27 Talbot height; Mildred W., —27 to —7 Boothby = —16 to +12 Talbot; Dorothy W., —20 to —8 Boothby = —15 to —1 Talbot; Marilyn M., —12 to —4 Boothby = —6 to +5 Talbot; Josephine L., —16 to +11 Boothby = —11 to +18 Talbot; Julia F., —9 to +11 Boothby = —5 to +18 Talbot.

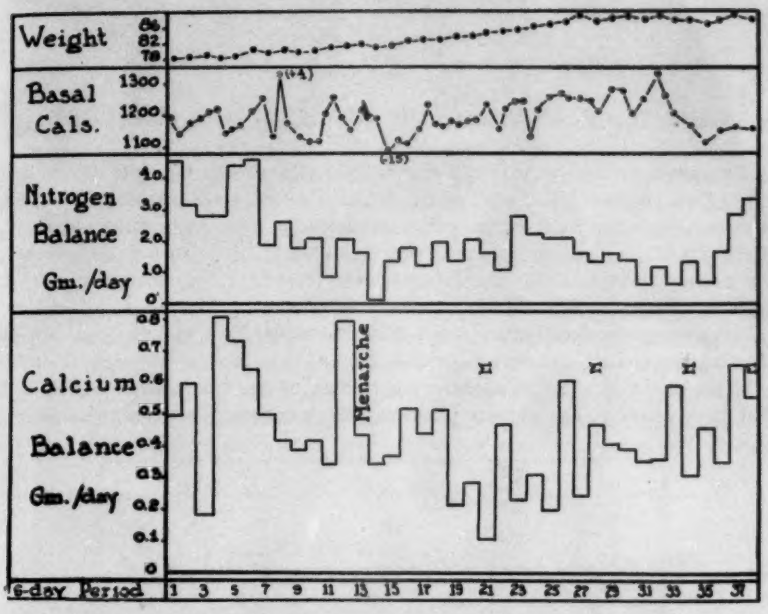


Chart 1 (Velma G.).—Continuous nitrogen and calcium balances plotted in six day periods for two hundred and twenty-eight days. The menarche occurred in the thirteenth period; subsequent menstrual periods are indicated by M. The extremes of the range of the basal metabolic rate are +4 per cent occurring just before the menarche, and —15 per cent, soon after.

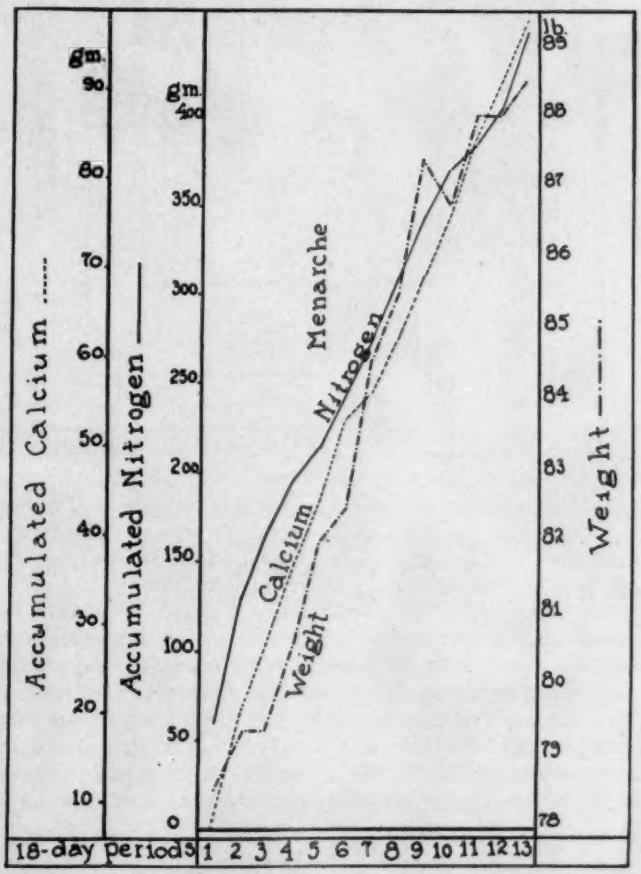


Chart 2 (Velma G.).—Cumulative nitrogen and calcium balances to show that in this patient there was a direct parallelism with weight gain.

The range of nitrogen retention was from a high of 4.61 Gm. per day to a low of 0.09 Gm. per day. The high figure occurred in the sixth period. The average retention of seventy-six days preceding the menarche was 2.69 Gm. per day. The lowest figure was obtained in the period immediately following the menarche. The average retention for one hundred and fifty days following the menarche was 1.57 Gm. per day.

The average calcium retention preceding the menarche was 0.495 Gm. per day; following the menarche it was 0.387 Gm. per day.

In the retention of nitrogen there was a more or less steady decline from somewhat high levels in the periods preceding the menarche, to a very low point in

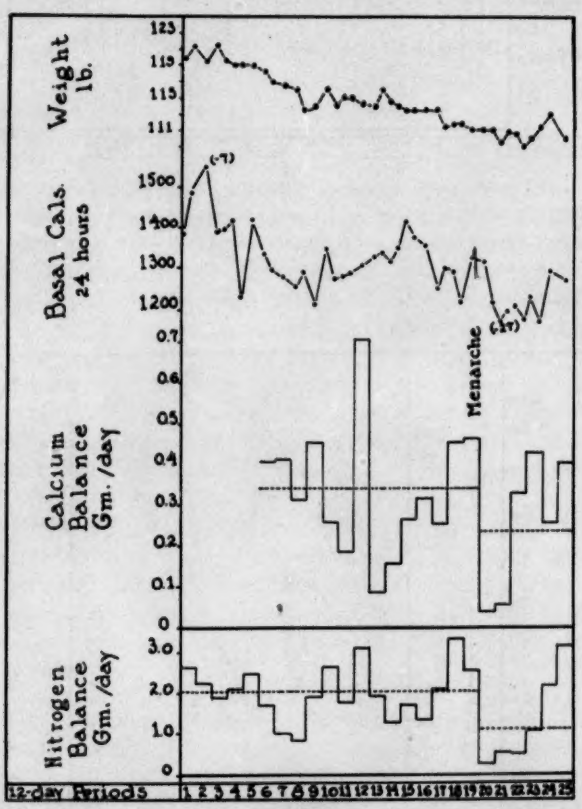


Chart 3 (Mildred W.).—Continuous nitrogen and calcium balances plotted in twelve day periods, nitrogen for three hundred days, calcium for two hundred and forty days. The weight showed a steady decline throughout. The basal metabolic rates ranged from —7 per cent in the second period to —27 per cent in the twenty-first period. The menarche occurred in the nineteenth period.

the period following the menarche. The menstrual loss was not included in the balance, but the error introduced must normally have been slight. An analysis of nine pads from an average menstrual period showed a nitrogen content of 0.09 Gm. per pad and a calcium content of 0.002 Gm. Unused pads averaged 0.01 Gm. of nitrogen and 0.001 Gm. of calcium. With calcium plotted in six day periods, there was a striking period to period variation, with a tendency to a cyclic pattern, but the longest periods of low retentions were from the nineteenth

through the twenty-fifth period, approximately a month following the first menstrual period. The retention per kilogram, on the basis of using the weight at the mid-points of the premenarcheal and postmenarcheal periods, was 66.4 mg. for nitrogen in the fore-period and 40.3 mg. in the after-period; for calcium, 13.6 mg. and 9.9 mg., respectively.

While the depression in nitrogen and calcium retention did not correlate exactly with the menarche, there was evident a sharp contrast in the retentions before and after this point. The recovery from this depression noted toward the end of the observation made it difficult to conceive of the trend in the comparatively simple manner that Robertson would have had one conceive of it; rather than being an expression of a depression incidental to the accumulation of end products

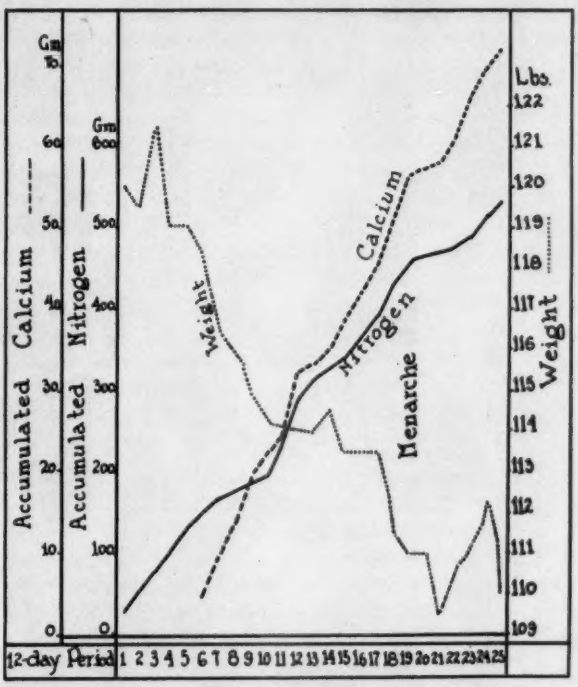


Chart 4 (Mildred W.).—Cumulative nitrogen and calcium balances to bring out that in this patient the consistent accumulation of nitrogen and calcium was compatible with a steadily declining weight curve.

of growth, the peak of his third "S curve," there was a suggestion that this recovery was the effect of the hormones influencing sexual development. Similar depressions did not accompany subsequent menstrual cycles.

Case 2.—Mildred W. (table 2, charts 3 and 4), a Negro girl 11 years old, was admitted to a sanatorium with a childhood type of tuberculosis in December 1937 and remained there until June 1, 1938, roentgen examination at that time showing nothing except some enlargement of the hilar nodes. At the time of her transfer to the Henry Ford Hospital for study, her weight was 120 pounds (54.4 Kg.), and her height was 62 inches (157.48 cm.), the estimated weight for that age and height being 104 pounds (47.2 Kg.). She attended two sessions of school, two

TABLE 2.—*Data for Mildred W.*

| 12 Day Periods | 1938-1939 Dates | Nitrogen, Gm. | | | | Retention, Mg. per Kg. | Calcium, Gm. | | | | Retention, Mg. per Kg. | Basal Metabolic Rate, Percentage | Respiratory Quotient | Calories per Square Meter per Hour | Basal Calories | Weight, Pounds | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Food Intake | Urine | Stool | Balance | | Food Intake | Urine | Stool | Balance | | | | | | | |
| 1 | 6/ 7-17 | 12.33 | 8.47 | 1.22 | +2.64 | .... | ..... | ..... | ..... | ..... | .... | −17 | 0.76 | 37.4 | 1,331 | 120 | |
| | | | | | | | | | | | | −11 | 0.71 | 40.1 | 1,481 | 121¼ | |
| 2 | 6/18-29 | 12.49 | 9.10 | 1.15 | +2.24 | .... | ..... | ..... | ..... | ..... | .... | − 7 | 0.75 | 42.3 | 1,552 | 119½ | |
| 3 | 6/30-7/11 | 12.39 | 9.54 | 0.97 | +1.88 | .... | ..... | ..... | ..... | ..... | .... | −16 | 0.74 | 37.7 | 1,394 | 121½ | |
| | | | | | | | | | | | | −15 | 0.75 | 37.9 | 1,399 | 119½ | |
| 4 | 7/12-23 | 12.20 | 9.13 | 0.97 | +2.10 | .... | ..... | ..... | ..... | ..... | .... | −15 | 0.74 | 38.3 | 1,416 | 119 | |
| | | | | | | | | | | | | −26 | 0.72 | 33.4 | 1,225 | 119 | |
| 5 | 7/24-8/4 | 12.21 | 8.82 | 0.93 | +2.45 | .... | ..... | ..... | ..... | ..... | .... | −14 | 0.77 | 38.6 | 1,419 | 119 | |
| 6 | 8/ 5-16 | 12.50 | 9.80 | 0.97 | +1.73 | .... | 1.180 | 0.041 | 0.733 | +0.406 | .... | −19 | 0.74 | 36.4 | 1,336 | 118¼ | |
| | | | | | | | | | | | | −21 | 0.75 | 35.4 | 1,292 | 117 | |
| 7 | 8/17-28 | 12.08 | 10.13 | 0.94 | +1.01 | .... | 1.130 | 0.006 | 0.714 | +0.410 | .... | −22 | 0.78 | 35.1 | 1,279 | 117 | |
| 8 | 8/29-9/9 | 12.13 | 10.12 | 1.19 | +0.82 | .... | 1.170 | 0.037 | 0.818 | +0.315 | .... | −24 | 0.77 | 34.4 | 1,254 | 116 | |
| | | | | | | | | | | | | −20 | 0.78 | 35.7 | 1,284 | 113½ | |
| 9 | 9/10-21 | 11.72 | 8.95 | 0.87 | +1.90 | .... | 1.140 | 0.017 | 0.670 | +0.453 | .... | −25 | 0.77 | 33.5 | 1,207 | 114 | |
| 10 | 9/22-10/3 | 12.81 | 9.00 | 1.19 | +2.62 | .... | 1.210 | 0.011 | 0.940 | +0.259 | .... | −18 | 0.79 | 37.2 | 1,346 | 116 | |
| | | | | | | | | | | | | −21 | 0.76 | 35.3 | 1,269 | 114 | |
| 11 | 10/ 4-15 | 12.00 | 9.37 | 1.44 | +1.79 | .... | 1.247 | 0.016 | 1.046 | +0.185 | .... | −22 | 0.85 | 35.0 | 1,270 | 115 | |
| | | | | | | | | | | | | −21 | 0.81 | 35.2 | 1,274 | 115 | |
| 12 | 10/16-27 | 12.56 | 8.82 | 0.62 | +3.12 | .... | 1.190 | 0.008 | 0.475 | +0.707 | .... | −19 | 0.78 | 36.0 | 1,304 | 114¼ | |
| 13 | 10/28-11/8 | 12.91 | 9.80 | 1.16 | +1.95 | .... | 1.170 | 0.013 | 1.070 | +0.087 | .... | −18 | 0.79 | 37.1 | 1,333 | 114 | |
| | | | | | | | | | | | | −18 | 0.71 | 37.0 | 1,339 | 116 | |
| 14 | 11/ 9-20 | 12.27 | 9.93 | 1.05 | +1.29 | .... | 1.112 | 0.013 | 0.940 | +0.159 | .... | −18 | 0.80 | 36.5 | 1,319 | 114½ | |
| | | | | | | | | | | | | −16 | 0.79 | 37.5 | 1,349 | 114 | |
| 15 | 11/21-12/2 | 12.93 | 10.26 | 0.97 | +1.70 | .... | 1.150 | 0.010 | 0.879 | +0.261 | .... | −11 | 0.73 | 39.4 | 1,419 | 113½ | |
| | | | | | | | | | | | | −15 | 0.79 | 38.3 | 1,377 | 113½ | |
| 16 | 12/ 3-14 | 12.54 | 10.03 | 1.12 | +1.39 | .... | 1.200 | 0.022 | 0.860 | +0.318 | .... | −16 | 0.75 | 37.7 | 1,358 | 113½ | |
| 17 | 12/15-26 | 12.64 | 9.44 | 1.11 | +2.09 | .... | 1.148 | 0.013 | 0.881 | +0.254 | .... | −22 | 0.74 | 34.7 | 1,250 | 113½ | |
| | | | | | | | | | | | .... | −19 | 0.76 | 36.4 | 1,300 | 111½ | |
| 18 | 12/27-1/7 | 12.82 | 8.56 | 0.96 | +3.30 | .... | 1.125 | 0.021 | 0.653 | +0.451 | .... | −19 | 0.83 | 36.0 | 1,286 | 111¾ | |
| | | | | | | | | | | | .... | −23 | 0.82 | 34.1 | 1,219 | 111¾ | |
| 19 | 1/ 8-19 | 13.12 | 9.69 | 0.88 | +2.55 | .... | 1.260 | 0.019 | 0.779 | +0.462 | .... | −17 | 0.79 | 37.0 | 1,323 | 111 | Menarche |
| | Average..... | | | | +2.02 | 38 | ..... | ..... | ..... | +0.340 | 6 | .... | .... | .... | ..... | 116 (52.7 Kg.) | |
| 20 | 1/20-31 | 11.35 | 10.01 | 1.09 | +0.25 | .... | 0.980 | 0.015 | 0.926 | +0.039 | .. . | −18 | 0.79 | 36.8 | 1,314 | 111 | |
| | | | | | | | | | | | | −23 | 0.83 | 34.0 | 1,216 | 111 | |
| 21 | 2/ 1-12 | 12.47 | 10.06 | 1.29 | +0.52 | .... | 1.173 | 0.008 | 1.113 | +0.052 | .... | −27 | 0.79 | 32.8 | 1,165 | 109½ | |
| | | | | | | | | | | | | −26 | 0.80 | 33.4 | 1,192 | 110¾ | |
| 22 | 2/13-24 | 12.29 | 10.71 | 1.07 | +0.51 | .... | 1.132 | 0.017 | 0.786 | +0.329 | .... | −25 | 0.78 | 33.9 | 1,205 | 110½ | |
| | | | | | | | | | | | | −25 | 0.82 | 33.4 | 1,177 | 109 | |
| 23 | 2/25-3/8 | 12.20 | 10.34 | 0.77 | +1.09 | .... | 1.100 | 0.005 | 0.669 | +0.426 | .... | −22 | 0.78 | 34.7 | 1,232 | 111 | |
| 24 | 3/ 9-20 | 12.58 | 9.32 | 1.07 | +2.19 | .... | 1.117 | 0.010 | 0.849 | +0.258 | .... | −27 | 0.81 | 32.5 | 1,169 | 112¼ | |
| | | | | | | | | | | | | −21 | 0.77 | 35.9 | 1,293 | 113 | |
| 25 | 3/21-26 | 12.60 | 8.45 | 0.98 | +3.17 | .... | 1.120 | 0.001 | 0.718 | +0.402 | .... | −21 | 0.77 | 35.7 | 1,267 | 110 | |
| | Average. ..... | | | | +1.12 | 22 | ..... | ..... | ..... | +0.237 | 4 | .... | .... | .... | ..... | 111 (50.2 Kg.) | |

hours in the morning and two in the afternoon, but she also had an hour's rest in the morning and in the afternoon.

The menarche occurred Jan. 18, 1939, lasted four days and was average in amount. The menstrual discharge was not included in the analysis.

An acute infection of the upper respiratory tract occurred on February 21 and 22, the temperature on the second day reaching 104 F. and then subsiding critically.

Throughout the entire observation the weight steadily declined from 118½ pounds (53.8 Kg.) to 114 pounds (51.7 Kg.).

The basal metabolism (table 2, chart 2) was almost constantly low, in keeping with what one would expect with diets sufficiently low to permit loss of weight, the highest rate being —7 per cent in the third period. The low point was reached in the second postmenarcheal period. The average basal metabolism of all the premenarcheal determinations was 1,332 calories per twenty-four hours; of all the postmenarcheal determinations, 1,223 calories per twenty-four hours.

Throughout the premenarcheal period, nitrogen retention ranged between 0.82 and 3.30 Gm., with an average of 2.02 Gm. The average retention per kilogram of body weight, all the weights of this period being averaged, was 38 mg. In the postmenarcheal period, the range of nitrogen retention was from 0.25 to 3.17 Gm.; the average, 1.12 Gm., and the retention per kilogram, calculated in the same way, 22 mg.

The calcium balance in the premenarcheal period, recorded in six day periods, showed a range between 0.087 and 0.707 Gm.; these two extreme figures, however, occurred in contiguous periods, and with these omitted, the range was narrower, 0.185 to 0.462 Gm. The average for the one hundred and fifty-four days of the premenarcheal period was 0.340 Gm. or 6 mg. per kilogram of body weight, the weight at the midpoint of the observation being used for the calculation. The range in the postmenarcheal period was from 0.039 to 0.426 Gm.; the average, 0.237 Gm., or 4 mg. per kilogram of body weight.

Case 3.—Dorothy W. (table 3, charts 5 and 6), a Negro, aged 10 years, was admitted to a sanatorium in October 1937 because on being checked as a contact she was shown to have a receding pleurisy and a homogeneous shadow, interpreted as representing a receding childhood type of tuberculosis, and she remained in that institution for nine months before being transferred to Henry Ford Hospital for study on June 1, 1938. A phrenic crushing had been done on the affected side.

Judged by weight, she was not as well nourished as the previous 2 children, being 4 pounds (1.8 Kg.) below the average weight for her age and height.

Her first menstrual period occurred on August 15, a second on September 12 and a third on October 5. During her stay she was afebrile and asymptomatic and attended the regular two sessions of school daily, but she did have rest periods of an hour each, morning and afternoon. During the study her weight declined from 101 to 95½ pounds (43.4 Kg.).

The basal metabolism for twenty-four hours rose from 1,298 calories (basal metabolic rate of —15 per cent) on admission to 1,411 calories (basal metabolic rate of —8 per cent) at the time of the menarche and then declined to 1,208 calories (basal metabolic rate of —20 per cent) thirty-six days later. Nitrogen retention ranged from 2.90 to 5.81 Gm. in the premenarcheal period, an average of 4.71 Gm. per day, or 105 mg. per kilogram of body weight. In the postmenarcheal period, it ranged from 1.06 to 2.85 Gm. per day during the twenty-eight days immediately following the menarche; then there was a single very high six day period of 6.07 Gm. The average for the sixty days following the menarche was 2.57 Gm., or 59 mg. per kilogram of body weight.

TABLE 3.—*Data for Dorothy W.*

| 6 Day Periods | 1938 Dates | Nitrogen, Gm. | | | | Retention, Mg. per Kg. | Calcium, Gm. | | | | Retention, Mg. per Kg. | Basal Metabolic Rate, Percentage | Respiratory Quotient | Calories per Square Meter per Hour | Basal Calories | Weight, Pounds | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Food Intake | Urine | Stool | Balance | | Food Intake | Urine | Stool | Balance | | | | | | | |
| 1 | 7/10-15 | 13.64 | 6.56 | 1.27 | +5.81 | .... | ..... | ..... | ..... | ..... | .... | —15 | 0.82 | 37.9 | 1,298 | 98½ | |
| 2 | 7/16-21 | 13.75 | 7.78 | 1.08 | +4.89 | | | | | | | | | | | | |
| 3 | 7/22-27 | 13.86 | 8.03 | 1.54 | +4.29 | .... | 1.320 | 0.060 | 0.760 | +0.500 | .... | —11 | 0.79 | 40.2 | 1,370 | 98½ | |
| 4 | 7/28-8/2 | 14.24 | 7.92 | 1.23 | +5.09 | .... | 1.353 | 0.059 | 0.617 | +0.678 | .... | —15 | 0.77 | 37.9 | 1,299 | 100 | |
| 5 | 8/ 2- 8 | 14.63 | 8.07 | 1.24 | +5.32 | .... | 1.386 | 0.061 | 0.655 | +0.670 | .... | — 9 | 0.82 | 40.7 | 1,386 | 98 | |
| 6 | 8/ 9-14 | 14.63 | 10.60 | 1.13 | +2.90 | .... | 1.386 | 0.073 | 0.640 | +0.673 | .... | — 8 | 0.84 | 41.4 | 1,411 | 97 | |
| | Average | | | | +4.71 | 105 | ..... | ..... | ..... | +0.649 | 14 | .... | .... | .... | ..... | 99 (44.8 Kg.) | |
| 7 | 8/15-20 | 14.08 | 10.77 | 1.41 | +1.90 | .... | 1.320 | 0.056 | 0.843 | +0.421 | .... | — 9 | 0.73 | 41.0 | 1,378 | 98½ | Menarche |
| 8 | 8/21-26 | 14.08 | 10.50 | 1.04 | +2.54 | .... | 1.320 | 0.055 | 0.600 | +0.665 | .... | —10 | 0.95 | 40.4 | 1,368 | 97 | |
| 9 | 8/27-9/1 | 14.08 | 10.10 | 1.18 | +2.80 | .... | 1.320 | 0.080 | 0.659 | +0.581 | .... | .... | .... | .... | ..... | .. | |
| 10 | 9/ 2- 7 | 14.08 | 11.25 | 1.43 | +1.40 | .... | 1.320 | 0.101 | 0.870 | +0.349 | .... | —12 | 0.89 | 39.4 | 1,343 | 97½ | |
| 11 | 9/ 8-13 | 14.08 | 11.65 | 1.37 | +1.06 | .... | 1.320 | 0.092 | 0.825 | +0.403 | .... | —20 | 0.86 | 36.1 | 1,221 | 96½ | |
| 12 | 9/14-19 | 14.08 | 11.27 | 1.39 | +1.42 | .... | 1.320 | 0.135 | 0.789 | +0.396 | .... | —20 | 0.88 | 36.0 | 1,208 | 95 | |
| 13 | 9/20-25 | 14.30 | 10.33 | 1.12 | +2.85 | .... | 1.364 | 0.150 | 0.616 | +0.598 | .... | —16 | 0.83 | 37.9 | 1,289 | 97½ | |
| 14 | 9/26-10/1 | 14.52 | 11.06 | 1.52 | +1.94 | .... | 1.408 | 0.167 | 0.898 | +0.343 | .... | —14 | 0.95 | 38.8 | 1,319 | 97 | |
| 15 | 10/ 2- 7 | 14.52 | 8.04 | 0.41 | +6.07 | .... | 1.408 | 0.000 | 0.112 | +1.296 | .... | —11 | 0.90 | 40.0 | 1,352 | 96½ | |
| 16 | 10/ 8-13 | 14.52 | 9.56 | 1.23 | +3.73 | .... | 1.408 | 0.097 | 0.680 | +0.631 | | | | | | | |
| | 10/14 | ..... | .... | .... | ..... | .... | ..... | ..... | ..... | ..... | .... | —16 | 0.85 | 37.9 | 1,282 | 95 | |
| | Average | | | | +2.57 | 59 | ..... | ..... | ..... | +0.460 | 10 | .... | .... | .... | ..... | 97 (43.9 Kg.) | |

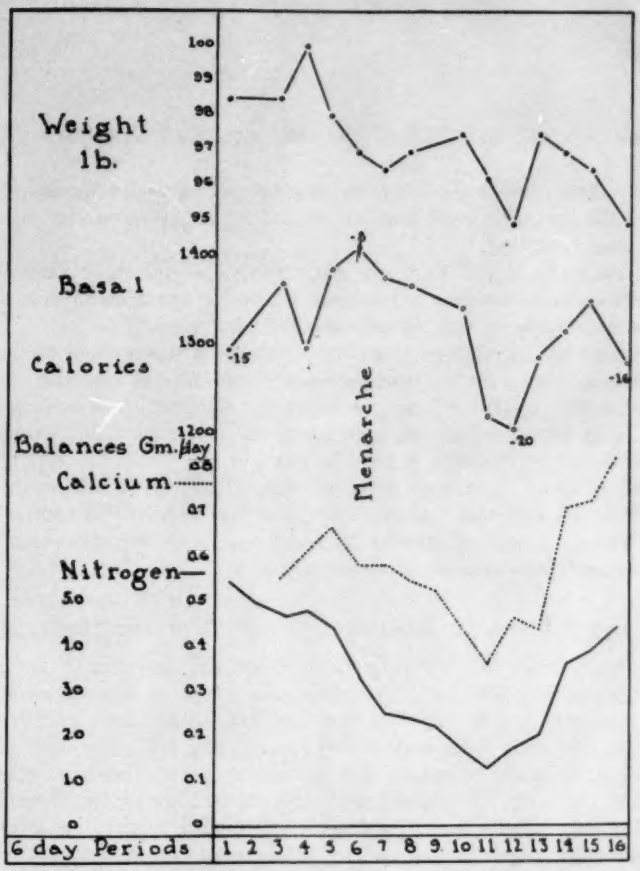


Chart 5 (Dorothy W.).—Continuous nitrogen and calcium balances plotted in curves smoothed by the method of 3's, six day balances being used. The menarche occurred in the sixth period. In this patient the low point in retention occurred thirty days after the menarche. There was a direct parallelism between the basal metabolic rate and retention, the higher retentions accompanying higher rates and vice versa. The weight declined steadily throughout the experiment.

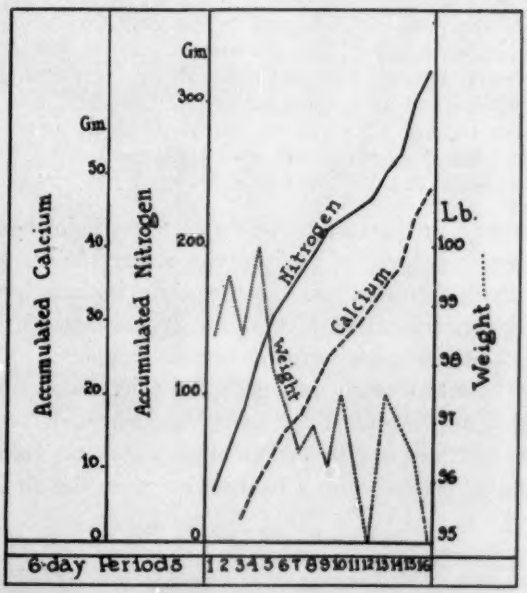


Chart 6 (Dorothy W.).—Cumulative nitrogen and calcium balances bring out the fact that in this patient also loss of weight was compatible with retention.

The average calcium retention per day before the menarche was 0.649 Gm. and after the menarche 0.460 Gm., or 14 and 10 mg., respectively, per kilogram of body weight per day.

From the chart it will be noted that although all metabolic rates were low, the correlation with nitrogen and calcium retentions was a direct one, the higher retentions accompanying the higher rates and vice versa.

The falling off in nitrogen retention in this child was evident in the six day period immediately preceding the menarche; the calcium retention declined in the period during which the menarche occurred. Menstrual flow was not analyzed, but any error introduced in this way would only accentuate this change.

While the entire metabolic pattern in this girl was similar to that of the previous two children, retentions were appreciably higher, which might best be explained by the fact that Dorothy's nutrition was impaired in comparison with that of Velma G. and of Mildred W., and that these retentions represent the well recognized replenishment of depleted stores.

### CHILDREN WITH A MINIMAL ADULT TYPE OF TUBERCULOSIS

CASE 4.—Marilyn M. (table 4, charts 7 and 8) was seen at the age of 12 years in November 1934 with a minimal adult type of tuberculous lesion. A grandmother gave the history that her diet had always been adequate in milk but that for the year previous to admission she had had very little meat. Her nutritional state judged by weight and appearance seemed excellent. She weighed 102 pounds (46.3 Kg.), compared with an estimated weight of 97 pounds (44.0 Kg.). She was afebrile and asymptomatic. Roentgen examination gave evidence of an unusually rapid healing of her tuberculous lesion, there being definite diminution in its size in a month after her admission.

For the first month of the study a diet of 2,200 calories with 14.75 Gm. of nitrogen was offered to her, but as some of this was either forced or refused, the dietary intake was dropped to 2,000 calories with 13.4 Gm. of nitrogen. For the first sixteen periods retention was comparatively high, averaging 1.52 Gm. per day, the peak being 3.5 Gm. throughout the fifth period. During this time healing was proceeding rapidly, as judged by roentgen examination.

Retention rapidly fell from then on, and for the next seventeen periods the average daily balance was 0.66 Gm., and during three periods of nine days the balance was actually negative. The menarche occurred during an attack of chickenpox, when collections were discontinued. A postmenarcheal period of twenty-seven days showed an average balance of 0.66 Gm. The basal metabolism ranged from between 1,260 calories (basal metabolic rate —12 per cent) and 1,477 calories (basal metabolic rate of —4 per cent) a day. Gain in weight was rapid, 21½ pounds (9.8 Kg.) in the year.

As will be seen in chart 7, the tendency to a diminished retention in this child began to be evident five months before the menarche, a relationship less direct than that noted in the other children, but it should be stressed again that the actual fact of the appearance of the menstrual flow is not an accurate measure of sexual maturity. The hormones operative are almost certainly active for considerable periods preceding and following this incident.

The case illustrates a type of retention which we have fairly consistently found associated with a healing lesion in the adolescent girl—

a steady mounting to very high levels, followed by a gradually declining retention. I have felt that this increased retention represents the replenishment of depleted reserves up to a saturation point, following

TABLE 4.—*Data for Marilyn M.*

| 9 Day Period | 1934-1935 Date | Nitrogen, Gm. Food Intake | Urine | Stool | Balance | Retention, Mg. per Kg. | Basal Metabolic Rate, % | Respiratory Quotient | Calories per Sq. Meter per Hour | Basal Calories | Wt., Lb. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11/13-21 | 14.20 | 11.52 | 1.62 | +1.00 | .... | —12 | 0.85 | 37.0 | 1,260 | 102 |
| 2 | 11/22-30 | 14.75 | 13.11 | 1.24 | +0.40 | | | | | | |
| 3 | 12/1-9 | 14.75 | 13.37 | 1.40 | —0.02 | | | | | | |
| 4 | 12/10-18 | 14.30 | 11.45 | 1.49 | +1.36 | | | | | | |
| 5* | 12/19-30 | 13.41 | 8.87 | 1.04 | +3.50 | | | | | | |
| 6 | 12/31-1/8 | 13.41 | 11.26 | 1.12 | +0.88 | .... | — 8 | 0.75 | 41.6 | 1,437 | 106½ |
| 7 | 1/15-23 | 13.41 | 10.59 | 1.36 | +1.46 | | | | | | |
| 8 | 1/24-2/1 | 13.41 | 10.52 | 0.74 | +2.15 | | | | | | |
| 9 | 2/ 2-10 | 13.41 | 9.87 | 1.13 | +2.42 | .... | — 7 | 0.78 | 39.0 | 1,375 | 111 |
| 10 | 2/11-19 | 13.41 | 10.65 | 1.23 | +1.53 | | | | | | |
| 11 | 2/20-28 | 13.41 | 10.07 | 1.06 | +2.28 | .... | —10 | 0.81 | 37.7 | 1,348 | 113 |
| 12 | 3/ 1-9 | 13.41 | 10.45 | 1.12 | +1.84 | | | | | | |
| 13 | 3/10-18 | 13.41 | 10.67 | 1.17 | +1.24 | .... | —13 | 0.84 | 36.7 | 1,330 | 114 |
| 14 | 3/19/27 | 13.41 | 10.23 | 1.32 | +1.18 | | | | | | |
| 15 | 3/28-4/5 | 13.41 | 10.94 | 1.10 | +1.37 | .... | —17 | 0.80 | 34.7 | 1,265 | 116¾ |
| 16 | 4/15-26 | 13.41 | 10.87 | 0.84 | +1.70 | .... | —13 | 0.81 | 36.6 | 1,335 | 118 |
| | | | | Average | +1.62 | | | | | | 112 (50.0 Kg.) |
| 17 | 4/27-5/5 | 13.41 | 11.58 | 0.97 | +0.88 | | | | | | |
| 18 | 5/ 6-14 | 13.41 | 11.46 | 1.30 | +0.65 | .... | —14 | 0.83 | 36.6 | 1,324 | 117½ |
| 19 | 5/15-23 | 13.41 | 11.88 | 1.30 | +0.23 | .... | — 4 | 0.78 | 40.3 | 1,470 | 116½ |
| 20 | 5/24-6/1 | 13.41 | 12.68 | 1.39 | —0.44 | | | | | | |
| 21 | 6/ 2-10 | 13.41 | 11.51 | 1.24 | +0.66 | .... | —18 | 0.79 | 34.5 | 1,266 | 118½ |
| 22 | 6/11-19 | 13.41 | 11.10 | 1.20 | +1.11 | | | | | | |
| 23 | 6/20-28 | 13.41 | 12.71 | 1.10 | —0.40 | .... | — 4 | 0.83 | 40.5 | 1,477 | 118½ |
| 24 | 6/29-7/7 | 13.41 | 12.52 | 1.27 | —0.38 | | | | | | |
| 25 | 7/ 8-16 | 13.41 | 11.61 | 1.16 | +0.64 | | | | | | |
| 26 | 7/17-25 | 13.41 | 11.57 | 1.16 | +0.67 | .... | — 8 | 0.79 | 38.7 | 1,430 | 117½ |
| 27 | 7/26-8/3 | 13.41 | 11.97 | 0.82 | +0.62 | .... | —18 | 0.78 | 34.3 | 1,271 | 118½ |
| 28 | 8/ 4-12 | 13.41 | 11.03 | 1.15 | +1.55 | | | | | | |
| 29 | 8/13-21 | 13.41 | 11.05 | 1.15 | +0.87 | .... | —12 | 0.77 | 37.0 | 1,376 | 119 |
| 30 | 8/22-30 | 13.41 | 11.08 | 1.05 | +1.28 | | | | | | |
| 31 | 8/31-9/8 | 13.41 | 12.26 | 1.15 | +0.33 | | | | | | |
| 32 | 9/ 9-17 | 13.41 | 12.17 | 1.18 | +0.06 | | | | | | |
| 33 | 9/18-23† | 13.41 | 10.55 | 1.19 | +1.67 | | | | | | |
| | | | | Average | +0.80 | 15 mg. | .... | .... | .... | ..... | 118 (53.2 Kg.) |
| | 9/24-10/20‡ | | | | | | | | | | |
| 34 | 10/21-29 | 13.41 | 10.51 | 1.12 | +1.78 | | | | | | |
| 35 | 10/30-11/7 | 13.41 | 11.29 | 1.48 | +0.64 | .... | —13 | 0.83 | 34.9 | 1,323 | 123½ |
| 36 | 11/ 8-16 | 13.41 | 12.83 | 1.00 | —0.42 | .... | —10 | 0.83 | 36.2 | 1,372 | |
| | | | | Average | +0.66 | 11 mg. | .... | .... | .... | ..... | 124 (55.9 Kg.) |

* Diet 2,000 calories.
† Six days. Study interrupted during varicella.
‡ Menarche at this time.

which diminished retentions are regularly encountered. I feel that the disease process in this child was no longer playing any role in the metabolism after the first few months and that it is logical to attribute the depressed retentions noted after that to the pubertal change.

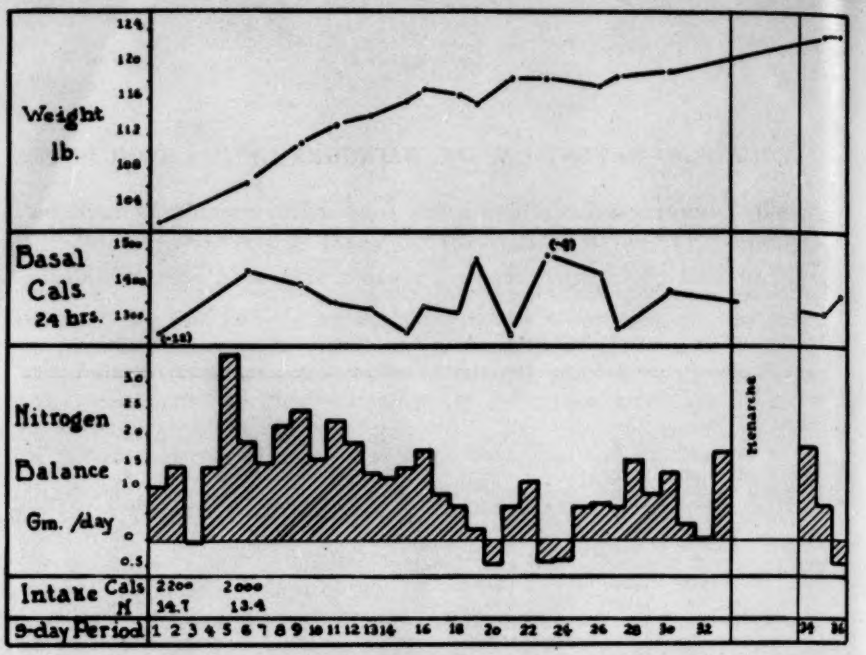


Chart 7 (Marilyn M.).—Continuous nitrogen balance for thirty-six periods of nine days. The study was interrupted from September 24 through October 20, during which the child had varicella and the menarche occurred. The falling off in retention was definite about the seventeenth period, approximately five months before the menarche.

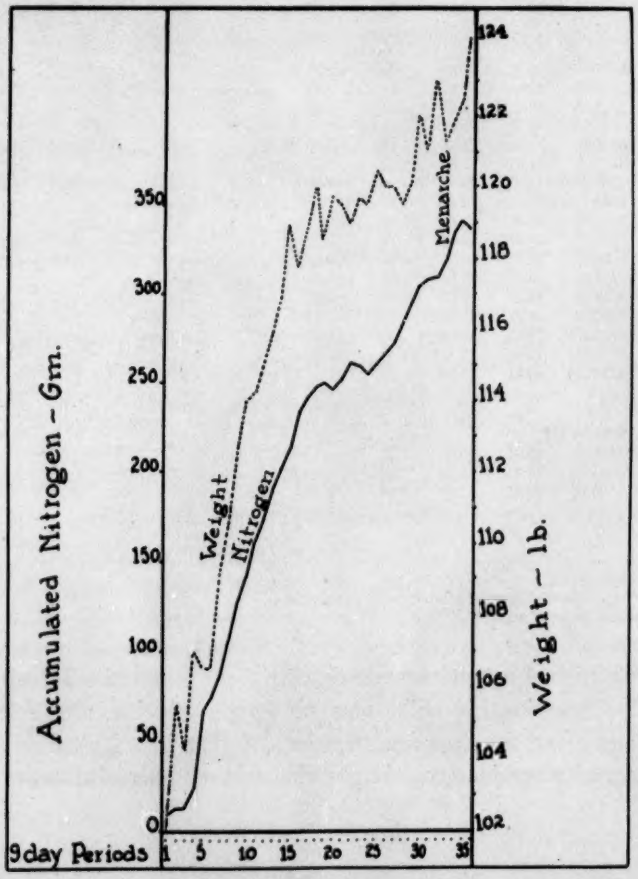


Chart 8 (Marilyn M.).—Continuous nitrogen balance plotted cumulatively against weight. The curves run parallel but diverge somewhat about the seventeenth period, suggesting that the increase in weight from then on was accompanied by a smaller percentage of nitrogen.

CASE 5.—Josephine L. (table 5, chart 9), a white girl aged 11 years, was first seen in May 1933, with a minimum adult type tuberculous lesion involving the upper lobe of the left lung. This lesion was not considered extensive enough to warrant collapse therapy. At that time she seemed definitely undernourished, weighing 72 pounds (32.7 Kg.), the estimated weight for an average girl of her height and age being 90 pounds (40.8 Kg.).

It was planned to study her food requirement in the manner outlined in a previous communication,[11] by varying the intake of both calories and protein, and to use the retention of nitrogen as a measure of the adequacy of her diet. The nitrogen balances recorded in this case were based on sporadic three day collections, and in chart 9 there have been listed the averages of three of these balances during the recorded dates. The observation extended from November

TABLE 5.—*Data for Josephine L.*

| Number | 9 Day Periods: Days | 9 Day Periods: 1934 | Nitrogen, Gm.: Output | Nitrogen, Gm.: Food Intake | Nitrogen, Gm.: Balance | Basal Metabolic Rate, % | Basal Calories | Weight, Pounds | Height, Inches | Diet: Calories | Diet: Percentage of Protein |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 9 | 11/26-12/11 | 12.80 | 12.00 | −0.80 | + 2 | 1,372 | 85 | 60¾ | 2,000 | 15 |
| 2 | 9 | 12/18-12/30 | 13.10 | 13.20 | +0.10 | .... | ..... | 87½ | .... | 2,200 | 15 |
| 3 | 9 | 1/ 4-1/12 | 12.16 | 13.20 | +1.04 | − 5 | 1,292 | .. | .... | 2,200 | 15 |
| 4 | 9 | 1/16-1/26 | 16.82 | 17.60 | +0.78 | − 3 | 1,342 | 90 | 61 | 2,200 | 20 |
| 5 | 9 | 2/ 4-2/13 | 19.30 | 22.00 | +2.70 | + 1 | 1,437 | 91½ | 61¼ | 2.200 | 25 |
| 6* | 6 | 2/22-2/26 | 11.72 | 11.44 | −0.28 | .... | ..... | 96 | .... | 2,200 | 13 |
| 7 | 9 | 3/ 7-3/28 | 13.04 | 11.44 | −1.60 | − 4 | 1,414 | .. | .... | 2,200 | 13 |
| 8† | 9 | 4/ 4-4/25 | 12.48 | 11.44 | −1.04 | − 4 | 1,408 | .. | .... | 2,200 | 13 |
| 9 | 9 | 4/28-5/6 | 12.50 | 13.20 | +0.61 | − 5 | 1,409 | 106 | .... | 2.200 | 15 |
| 10† | 9 | 5/14-5/27 | 15.39 | 13.20 | −2.19 | .... | ..... | ... | .... | 2,200 | 15 |
| 11 | 9 | 6/ 2/6/26 | 14.73 | 13.20 | −1.53 | − 2 | 1,443 | 110 | .... | 2.200 | 15 |
| 12 | 9 | 6/27-7/14 | 15.35 | 13.20 | −2.15 | +11 | 1.655 | ... | 62¼ | 2,200 | 15 |
| 13 | 8 | 7/15-7/22 | 14.24 | 13.20 | −1.04 | | | | | | |
| 14† | 9 | 7/23-8/2 | 14.39 | 13.20 | −1.19 | −10 | 1,358 | 110 | 62¼ | 2,200 | 15 |
| 15 | 9 | 8/ 3-8/11 | 13.58 | 13.20 | −0.38 | −16 | 1,258 | 112 | .... | 2,200 | 15 |
| 16 | 9 | 8/12-8/20 | 15.58 | 13.20 | −2.38 | + 5 | 1,574 | ... | .... | 2,200 | 15 |
| 17 | 8 | 8/21-9/2 | 13.81 | 13.20 | −0.61 | .... | ..... | ... | .... | 2,200 | 15 |
| 18† | 9 | 9/ 5-9/16 | 14.42 | 13.20 | −1.22 | .... | ..... | ... | .... | 2,200 | 15 |
| 19 | 9 | 9/20-9/28 | 13.19 | 13.20 | +0.01 | .... | ..... | ... | .... | 2,200 | 15 |
| 20 | 9 | 10/ 8-10/16 | 11.76 | 13.20 | +1.44 | − 4 | 1.451 | 110 | 62¾ | 2,200 | 15 |

* Menarche.
† Menses.

1934 to October 1935, but the actual number of days during which collections were made was only one hundred and seventy-five. While the dietary intake was varied, identical intakes will be noted in January, one month before the menarche, which occurred on February 15, and in the months from April to October. Gain in weight was rapid from November 1934 to August 1935, 27 pounds (12.2 Kg.). With a diet providing calories adequate for this rapid gain, and with which positive balances had been obtained before the menarche, the balances were negative almost constantly from February 22 to September 20. There was an abrupt increase in the basal metabolism in June, which coincided with the extension of the disease process, and collapse therapy was accompanied by an apparent fall in metabolic rate, but this decline was difficult to evaluate until adjustment to the diminished lung capacity had taken place.

The course of the tuberculous lesion in the chest as judged by roentgen examination was as follows: From May 1933 through December 1934, the lesion seemed to be stationary; in February there was noted a slight increase, and the plate in July showed so marked a change that collapse therapy was immediately instituted.

It is, of course, impossible to say that the negative balances in this case were in the nature of a cause rather than an effect of the increase in the disease, but in view of the definitely established suppression of retention in the cases of Velma G., Dorothy W. and Mildred W. incidental to the menarche, it is reasonable to infer that in this case sexual maturation was a major factor diminishing retention, and that this in turn favored the spread of the disease.

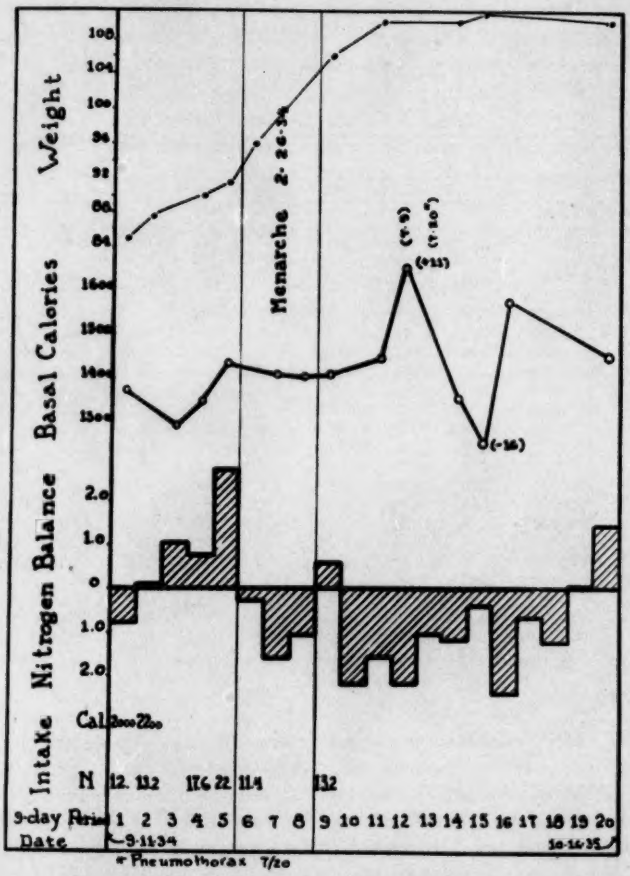


Chart 9 (Josephine L.).—Continuous nitrogen balance for one hundred and eighty days plotted in nine day periods, in the seventh of which the menarche occurred. The child had a minimal adult type of tuberculosis. The intake varies for reasons stated in text, but it will be noted that on the amounts that produced a positive balance in the premenarcheal period, negative balances occur following the menarche. A frank spread of the tuberculous process was detected about the twelfth period, and pneumothorax was instituted with ultimate recovery.

CASE 6.—Julia F. (table 6, chart 10), born Dec. 29, 1923, was removed from her mother's care in February 1934 when her mother was hospitalized for tuber-

culosis. At that time she reacted to tuberculin and showed a calcified gland in the hilus of the right lung, but the parenchyma of the lung was clear. In October 1934, in the course of a regular examination, a lesion interpreted as being of an adult type was detected in the apex of the left lung and she was hospitalized; the studies to be reported were conducted almost continuously for the next eighteen months. This was not planned as a study of the reaction at puberty but was rather an attempt to estimate, by means of the method described in a previous communication,[11] the protein requirement of this type of child. Accord-

TABLE 6.—*Data for Julia F.*

| Caloric Intake | No. of Days* | Dates | Nitrogen, Gm. | | | | | Basal Metabolic Rate, % | Respiratory Quotient | Basal Calories | Weight, Pounds |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Urine | Stool | Output | Food Intake | Balance | | | | |
| | | 1934 | | | | | | | | | |
| 2,200 | 3 | 10/29-10/31 | 10.33 | 0.98 | 11.31 | 12.88 | +1.57 | + 3 | 0.90 | 1,212 | 65 |
| 1,650 | 29 | 11/10-12/12 | 10.32 | 1.19 | 11.51 | 10.00 | —1.51 | + 6 | 0.82 | 1,284 | 66¼ |
| 1,800 | 19 | 12/13- 1/ 2 | 10.14 | 1.15 | 11.29 | 12.07 | +0.78 | | | | |
| | | 1935 | | | | | | | | | |
| 1,700 | 30 | 1/24-3/4 | 8.74 | 1.33 | 10.07 | 11.40 | +1.33 | + 7 | 0.78 | 1,330 | 72½ |
| | | | | | | | | +11 | 0.80 | 1,380 | 72½ |
| 1,700 | 30 | 3/5-4/4 | 8.91 | 1.32 | 10.32 | 10.40 | +1.17 | — 1 | 0.82 | 1,272 | 74½ |
| | | | | | | | | + 2 | 0.82 | 1,310 | 74½ |
| 1,700 | 42 | 4/5-5/23 | 9.99 | 1.43 | 11.42 | 11.40 | —0.02 | — 2 | 0.82 | 1,267 | 76¾ |
| | | | | | | | | ± 0 | 0.81 | 1,296 | 77 |
| | | | | | | | | + 1 | 0.81 | 1,308 | 76½ |
| 1,700 | 34 | 5/24-6/29 | 11.06 | 1.13 | 12.19 | 11.40 | —0.79 | + 1 | 0.84 | 1,308 | 76¾ |
| | | | | | | | | + 4 | 0.80 | 1,366 | 77 |
| 1,700 | 33 | 6/30-8/3 | 11.20 | 1.24 | 12.50 | 11.40 | —1.10 | — 1 | 0.80 | 1,305 | 77½ |
| | | | | | | | | + 2 | 0.78 | 1,327 | 76½ |
| 1,700 | 30 | 8/4-9/2 | 10.62 | 1.13 | 11.75 | 11.40 | —0.35 | | | | |
| 1,700 | 30 | 9/3-10/3 | 10.66 | 1.20 | 11.86 | 11.40 | —0.46 | — 7 | 0.81 | 1,292 | 78½ |
| | | | | | | | | — 9 | 0.84 | 1,216 | 80¾ |
| 1,700 | 30 | 10/6-11/4 | 10.44 | 1.18 | 11.62 | 11.40 | —0.22 | — 3 | 0.94 | 1,297 | 81 |
| Menarche | | | | | | | | | | | |
| 2,200 | 27 | 11/5-2/9 | 13.34 | 1.42 | 14.76 | 14.75 | —0.01 | ± 0 | 0.85 | 1,336 | 80 |
| | | | | | | | | — 3 | 0.82 | 1,359 | 83¾ |
| | | 1936 | | | | | | | | | |
| 2,200 | 33 | 2/10-3/21 | 11.61 | 1.38 | 12.99 | 14.75 | +1.76 | + 4 | 0.81 | 1,457 | 87¼ |
| | | | | | | | | — 1 | 0.85 | 1,387 | 88¾ |
| | | | | | | | | + 5 | 0.82 | 1,495 | 89½ |
| | | | | | | | | ± 0 | 0.85 | 1,421 | 90¾ |
| 2,200 | 33 | 3/22-5/1 | 11.37 | 1.33 | 12.70 | 14.75 | +2.05 | ± 0 | 0.80 | 1,421 | 95 |

* Number of days during which the balance was determined. The balance was determined continuously from Jan. 24, 1935, through March 21, 1936.

ingly, several levels of intake will be noted from October to January. It was our plan to give an amount of food that would be taken without forcing and that would result both in good weight gain and in a positive nitrogen balance. When these criteria seemed fulfilled with an intake of 1,700 calories with 11.4 Gm. of nitrogen, no change in intake was made from Jan. 24, 1935, through October 1935. It will be noted from chart 10 and table 6 that the nitrogen balance was positive until May, when it became negative, in spite of which the patient continued to gain consistently in weight until August, when there was a temporary decline. During the period of positive balances, the basal metabolic rates ranged between —2 and + 11 per cent; from May until November, during which time the nitrogen balances were negative, the range of the basal metabolic rate was between

± 4 and —9 per cent. At this time the dietary intake was increased to 2,200 calories with 14.75 Gm. of nitrogen; the balances became strongly positive, and the metabolic rate ranged between —3 and + 5 per cent.

The first menstrual period occurred on Dec. 27, 1935, and subsequent ones occurred on February 26, March 30 and May 3, 1936.

The roentgenograms read by several observers were interpreted as showing a minimal lesion in February 1935, an essentially unchanged picture in April, but a more extensive shadow in August. No further advance was noted after this date, however, and the plates of June 1936 showed a small quiescent lesion, which was beginning to calcify.

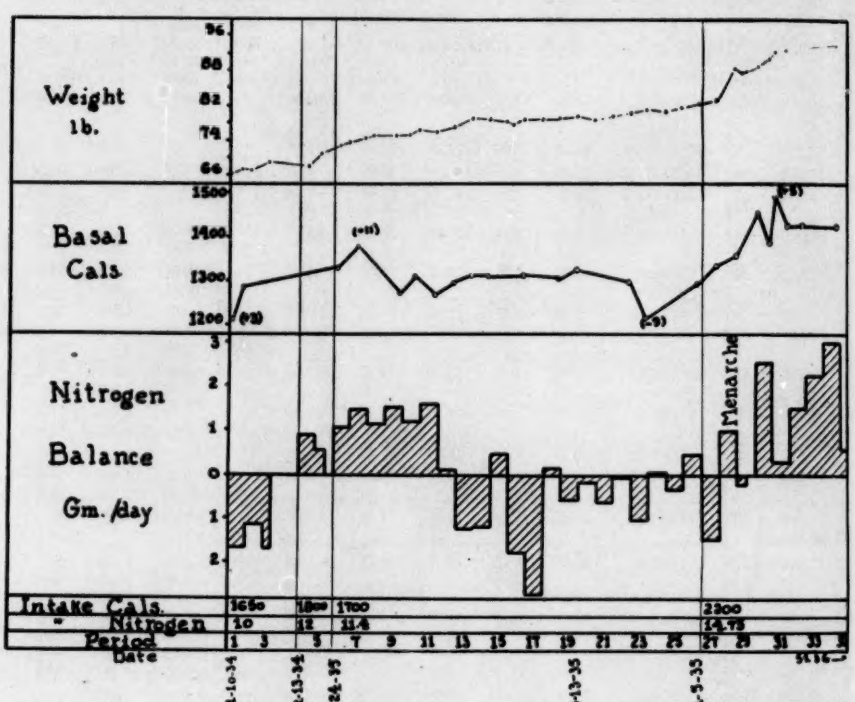


Chart 10 (Julia F.).—Continuous nitrogen balance in a child with minimal tuberculosis. The balance is practically continuous for eighteen months and is for the most part plotted in twelve day periods. A few interruptions are recorded in the table and indicated in the chart by breaks. Various levels of intake are indicated, but diet was constant from the sixth through the twenty-sixth periods, or from Jan. 24, 1935, through Nov. 4, 1935. A slight increase in the roentgen evidence of the tuberculous process was detected in the twentieth period.

Three variables have made the interpretation of these data difficult. First, the phase of negative balance between May and November might have been due to the fact that the patient had grown beyond the adequacy of a diet that had fulfilled her requirements in the previous five months.

This was unlikely, as some extensive studies on this point [7] have shown that the reaction to an inadequate intake rather consistently involves falls in the basal metabolic rate to levels in the neighborhood of —20 to —25 per cent. Of course, her rates may have been the resultant of a tendency in this direction which was being offset by the premenarcheal rise. Second, the depression might have been due to the proximity of the menarche. Third, it might have been due to the extension of her disease process. All things considered, however, the fact that there was no advance in her disease process from October 1934 to May 1935, when she was retaining nitrogen adequately, plus my knowledge of the depressing effect of the phenomena of sexual maturation on retention, has made me feel that the reasonable interpretation of the entire picture would be that the pubertal change, with its attendant metabolic depression in retention, favored the spread of the disease and that this decrease in retention could be offset by an increase in the dietary intake.

In the 3 cases of normal children presented, the diminution in retention did not reach the point of actual negative balances, but the dietary intakes were apparently more adequate. This case probably represents what may take place under unfavorable circumstances of diet.

## COMMENT

The essential finding in this study is that sexual maturation in the girls studied carried with it a depression in the retention of calcium and nitrogen. It is not felt that the incident of the menarche itself marks definitely the precise time at which this occurs; rather this incident is merely one of the phenomena marking this phase of the growth period, and the diminution in retention may precede or follow it by months.

Regarding the possible relationship of this finding to the increased incidence of the reinfection type of tuberculosis in a girl at this age, it is not claimed that the material presented here represents more than highly suggestive data favoring the idea that diminution of reserves as a result of this phenomenon may be a contributing factor. It is evident that the diminished retention may be prevented from reaching the point of actual negative balances by maintaining the dietary intake at sufficiently high levels. For nitrogen the requirements would seem to be definitely established; the protein intake should probably be 15 per cent of the calories when these are adequate. The calcium intake of the three normal girls studied, all of whom retained a positive balance, was approximately 1,200 mg. per day for Velma G. and Mildred W. and 1,380 mg. per day for Dorothy W.; but whether or not these amounts are minimal or optimal requires further study. No source of vitamin D was specifically provided.

The physiologic rise and fall of the basal metabolic rate at the pubertal period are confirmed, but it is not felt that these two phases of basal metabolism are separated consistently by the menarche. Retention parallels the metabolic rate, the higher rates accompanying the higher retentions and vice versa. This is apparently a phenomenon of the period of growth. When growth ceases, lower metabolic rates would seem to be accompanied by higher retentions, and vice versa. Within limits, this normal phenomenon may be ignored. Many instances are encountered clinically, however, in which this physiologic tendency becomes pathologic, and particularly in view of the findings made by Maroney and me on the relation of thyroid to the retention of calcium,[12b] it would seem logical not to dismiss these deviations expectantly but to treat them. My associate and I have seen the premenarcheal rise in basal metabolism accompanied by the toxic manifestations of hyperthyroidism, and with the institution of iodine therapy and rest in bed we have seen a prompt fall in the metabolic rate with the onset of the menses. Conversely, when the depressed phase of the cyclic change reaches levels which are accepted as pathologically low, the administration of thyroid not only gives symptomatic relief but has the further indication that retention will be improved. In this connection, the amount of thyroid to be administered is highly important; amounts sufficient to elevate the metabolic rate to normal limits should improve retention; larger amounts should diminish it; hence the injunction to administer "to tolerance" should carry with it a clearcut definition of what the term involves. It must be admitted, however, that in the study which I have presented in this report, factors other than the thyroid, notably diet and diminished activity, have conditioned the metabolic rate, and it is true that retentions have been recorded here which my associate and I did not find when correspondingly low rates existed in the thyroid study referred to. I have found, however, that retentions accompanying the lowered metabolic rates attendant on prolonged rest in bed can be elevated in a child by administering thyroid. This finding will be the subject of a separate report.

## CONCLUSIONS AND SUMMARY

Sexual maturity in the girl is accompanied by a depression in the retention of calcium and nitrogen.

A physiologic rise and fall in the metabolic rate at this period are confirmed.

The parallelism between retention and metabolic rate at this period is a direct one; the higher the rate within normal limits, the higher is the retention, and vice versa. This is the reverse of the situation in the adult with respect to calcium, as judged by the literature.

Possible implications of these findings in relation to the increase in the reinfection type of tuberculosis in the girl at this age period are discussed. Essentially, the data suggest that the depressing effect of the phenomenon of puberty in the girl may constitute one factor diminishing the retention of calcium and nitrogen and that this has an unfavorable effect on the course of tuberculosis.

Dr. Frank Hartmann supervised the determinations of basal metabolism and Dr. O. H. Gaebler the nitrogen and calcium determinations.

Dr. John W. Maroney assisted with the earlier cases; Dr. Stuart Willis referred suitable subjects for study to me, and Mrs. R. McLeod helped in the charting.

# USE OF COMBINATION MICROHEMOPIPET

## WITH SPECIAL REFERENCE TO SEDIMENTATION RATE, PACKED CELL VOLUME AND ICTERIC INDEX IN PEDIATRIC PRACTICE

KATSUJI KATO, M.D., PH.D.
CHICAGO

The use of the newly devised combination microhemopipet, elsewhere described (Kato [1]), facilitates the simultaneous determinations of the erythrocyte sedimentation rate, the packed cell volume and the icteric index with an amount of blood small enough (50 cu.mm.) to be easily obtained by the capillary puncture method used in routine examinations of the blood. The arguments in favor of using capillary blood in preference to venous blood for these tests have been repeatedly discussed by numerous authors, so that a reiteration of its advantages at this time is superfluous; nor is it necessary to summarize the various types of micropipets or tubes now steadily multiplying on the market. Mention should be made, however, of the micromethod recently devised by Smith,[2] which may be regarded as a microadaptation of the Wintrobe tube (Wintrobe [3]), with the addition of a mixing pipet. Exhaustive reviews, particularly of the various methods for the sedimentation test, are found in papers by Fischel,[4] Katz and Leffkowitz,[5] Westergren [6]

From the Department of Pediatrics, University of Chicago.

Read at the Conference of Clinical Laboratory Technicians, Tri-State Hospital Assembly, May 5, 1939.

The combination microhemopipets, metal holders and specially designed rack with an icteric index comparator scale are now obtainable from Fisher Scientific Co., 711 Forbes St., Pittsburgh.

1. Kato, K.: Combination Microhemopipette, J. Lab. & Clin. Med. **23**:980, 1938.

2. Smith, C. H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children with the Use of Capillary Blood, Am. J. M. Sc. **192**:73, 1936.

3. Wintrobe, M. M.: A Simple and Accurate Hematocrit, J. Lab. & Clin. Med. **15**:287, 1929.

4. Fischel, K.: The Suspension Stability Rate of Erythrocytes in Pulmonary Tuberculosis and Its Significance in Artificial Pneumothorax, Am. Rev. Tuberc. **10**:606, 1925.

5. Katz, G., and Leffkowitz, M.: Die Blutkörperchensenkung, Ergebn. d. inn. Med. u. Kinderh. **33**:266, 1928.

6. Westergren, A.: Die Senkungsreaktion, Ergebn. d. inn. Med. u. Kinderh. **26**:577, 1924.

and Wintrobe.[7] The purpose of the present communication is simply to describe in detail the exact technic developed in the use of the combination microhemopipet and to report some of the more significant results of actual determinations, which may serve as tentative standards for both normal and pathologic blood.

It is known that the most important factors influencing the suspension stability and the packed cell volume of erythrocytes in health and disease are (1) the activity of the disease; (2) the level of plasma proteins and lipids, particularly fibrinogen, globulin and cholesterol; (3) anemias, because of their effects on the size and number of the red blood cells, and (4) the coagulability, together with isoagglutination and rouleau formation, of the blood. The first three factors are inherent in the blood itself, being the very objects of determination; but the last-named factor can be controlled by the employment, in proper amounts, of a suitable anticoagulant. Naturally this factor is negligible in hemophilic blood, the coagulation time of which is often prolonged beyond one hour. But with the majority of samples adequate precaution must be taken to render the blood absolutely noncoagulable. First of all, then, it is of paramount importance to know the effects on the blood, particularly on the erythrocytes, of the most commonly used anticoagulants.

## CHOICE OF ANTICOAGULANTS

In order to determine the most satisfactory anticoagulants which may safely be used in the manner recommended for the performance of the tests in question, a series of observations were made, the results of which are presented in table 1. As anticoagulants in aqueous solutions introduce complicating factors such as dilution of the blood and possible hemolysis, all anticoagulants used in these studies were mixed in dry form with stated amounts of blood.

As the data here presented reveal, the most striking feature of various anticoagulants is their influence on the packed cell volume of the blood. As a rule the greatest expansion, or swelling, of the erythrocytes occurs when the blood is treated with ammonium oxalate, while potassium oxalate, on the contrary, causes the maximum shrinkage of these cells. In fact the degree of shrinkage occasioned by the use of potassium salt, according to the results of present observations, is above that obtained with the use of heparin, the cell volume usually being considerably more than 7 per cent lower with the former. Treating the blood with sodium oxalate or sodium citrate frequently produces a decided shrinkage, almost equal in degree to that seen with

7. Wintrobe, M. M.: Erythrocyte Sedimentation Test, Internat. Clin. **2**:34, 1936.

potassium oxalate. The sedimentation rate, however, appears to be somewhat independent of the effects of these anticoagulants, although it is to be noted that the rate is rather consistently low with ammonium oxalate and frequently high with potassium oxalate, suggesting a possible relation between the cell volume and the suspension stability.

The undesirable effects of single oxalates on the blood cells have been overcome by Heller and Paul [8] in their discovery that by mixing ammonium oxalate and potassium oxalate in proper proportions the

TABLE 1.—*Effect of Various Anticoagulants on Packed Cell Volumes in Blood of a Patient with Thrombocytopenic Purpura* *

| Date | Red Cells, Million per Cu. Mm. | Hemoglobin, Gm. per 100 Cc. | Platelets per Cu. Mm. | Packed Cell Volumes, Percentage | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Heparin | Liquoid† | Double Oxalate‡ | Sodium Oxalate | Ammonium Oxalate | Potassium Oxalate |
| 12/ 3/38 | 4.03 | 7.8 | 80,000 | 30 | .. | 28 | 23 | 33 | 22 |
| Transfusions | | | | | | | | | |
| 12/ 8/38 | 4.38 | 7.5 | 110,000 | 29 | 31 | 28 | 21 | 35 | 23 |
| 12/10/38 | 4.98 | 7.5 | 90,000 | 31 | 34 | 31 | .. | .. | .. |
| 12/14/38 | 4.55 | 9.2 | 90,000 | 33 | 35 | 31 | 27 | 34 | 27 |
| Transfusions | | | | | | | | | |
| 12/19/38 | 5.45 | 8.6 | 90,000 | 36 | 37 | 34 | .. | .. | .. |
| Discharged as improved | | | | | | | | | |
| 3/30/39 | 4.07 | 9.8 | 100,000 | 36 | .. | .. | .. | .. | .. |
| 4/ 3/39 | 4.60 | 10.8 | 90,000 | 36 | 36 | 35 | 33 | 40 | 33 |
| 4/ 9/39 | 3.86 | 10.5 | 65,000 | 34 | 34 | 33 | 29 | 39 | 28 |
| 4/10/39 Splenectomy and transfusions | | | | | | | | | |
| 4/11/39 | 5.07 | 13.0 | 155,000 | 44 | 45 | 45 | 37 | 51 | 37 |
| 4/13/39 | 4.85 | 13.4 | 220,000 | 43 | 44 | 43 | 36 | 49 | 34 |
| 4/15/39 | 5.18 | 14.2 | 195,000 | 44 | 44 | 39 | .. | .. | .. |
| Hemolytic streptococcic otitis media | | | | | | | | | |
| 4/18/39 | 5.00 | 12.8 | 175,000 | 44 | 45 | 45 | 41 | 51 | .. |
| 4/21/39 | 5.58 | 14.2 | 155,000 | 44 | 46 | 46 | 38 | 52 | 40 |
| 4/23/39 | 5.47 | 13.8 | 220,000 | 45 | 45 | 45 | 40 | 49 | 41 |
| 4/24/39 | 6.32 | 13.0 | 260,000 | 46 | 45 | 44 | 39 | 52 | 40 |

* Combination microhemopipet method.
† Sodium polyanetholsulfonate.
‡ Ammonium and potassium oxalates (Heller and Paul [8]).

packed cell volumes approximated those obtained with heparin. The composition of this mixture, as recommended by its originators and as modified by the present observations, is given in the tabulation.

| | Heller and Paul | Kato |
|---|---|---|
| Ammonium oxalate | 1.2 Gm. | 1.25 Gm. |
| Potassium oxalate | 0.8 Gm. | 0.75 Gm. |
| Distilled water | 100.0 cc. | 100.00 cc. |

8. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777, 1934.

The most ideal anticoagulants, however, are heparin and sodium polyanetholsulfonate.[9] Both of these anticoagulants produce little alteration in the size or shape of the erythrocytes, as checked by the comparison of measurements of average normal red blood cells on stained smears made from samples of blood treated with the various anticoagulants studied (fig. 1). Heparin acts as an antithrombase, according to Best,[10] while the action of sodium polyanetholsulfonate depends primarily on molecular size rather than on chemical structure (Demole and Reinert[11]).

The most effective quantity of anticoagulant to be used for a test is somewhat subject to variation, as even under normal conditions the blood differs considerably in cellular as well as in chemical composition. But actual experience proves 1 mg. of heparin, liquoid or double oxalate mixture to be sufficient to keep 1 cc. of

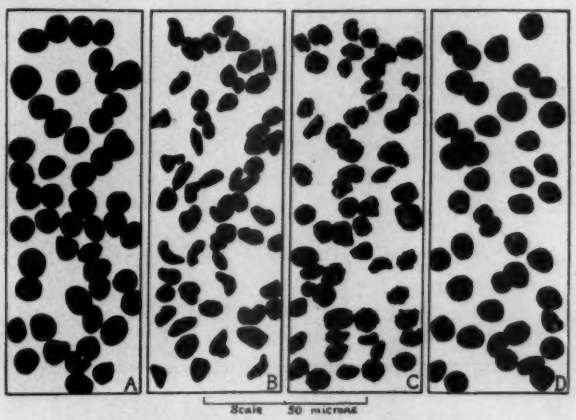


Fig. 1.—Camera lucida drawings of erythrocytes from stained smears of packed cells after treatment with various anticoagulants: *A*, ammonium oxalate; *B*, sodium citrate; *C*, potassium oxalate, and *D*, heparin. Note the scale of magnification at the bottom of the figure.

average normal human blood in fluid condition for several hours, the proportion thus being 1:1,000. In practice, to insure the noncoagulation of the blood, it is advisable to use an excess of anticoagulant, for example, double the quantity

9. The crude form of heparin, sufficiently potent for hematologic work, is obtainable from the Connaught Laboratories, University of Toronto, Toronto, Canada, or from Hynson, Westcott and Dunning, Baltimore. The sodium salt of polyanethosulfonic acid is marketed in a synthetic form by Hoffmann-LaRoche, Inc., Nutley, N. J., under the trade name of liquoid "Roche."

10. Best, C. H.: Heparin and Thrombosis, Proc. Inst. Med. Chicago **12**:210, 1938.

11. Demole, V., and Reinert, M.: Polyanetholsulfosaures Natrium, ein neues synthetisches Mittel zur Hemmung der Blutgerinnung, Arch. f. exper. Path. u. Pharmakol. **158**:211, 1930.

(1:500). Since 0.2 cc. is the maximum amount of blood required for the purpose of making all the determinations, the actual amount of anticoagulant to be used is less than 0.4 mg.

The anticoagulants are best prepared in stock solutions, with 1 per cent concentration for heparin and sodium polyanetholsulfonate.[9] All stock solutions must be kept in the refrigerator and filtered at frequent intervals.

## METHOD OF OBTAINING BLOOD

As a receptacle for the samples of blood, a hanging drop slide with a central circular depression measuring 15 mm. in diameter and 3 mm. in depth is recommended. Into this depression is transferred, by means of a combination micropipet, exactly 20 cu. mm. of a 1 per cent solution of either heparin or liquoid. For the 2 per cent solution of double oxalate mixture the same amount is recommended,

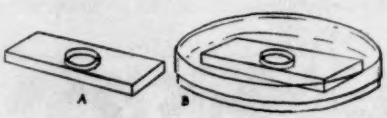

Fig. 2.—*A*, hanging drop slide with a central depression (15 mm. in diameter and 3 mm. in depth) used as a receptacle for a sample of blood; *B*, moist chamber, made by placing wet filter paper in bottom of a Petri dish, in which is placed the slide containing the sample of blood.

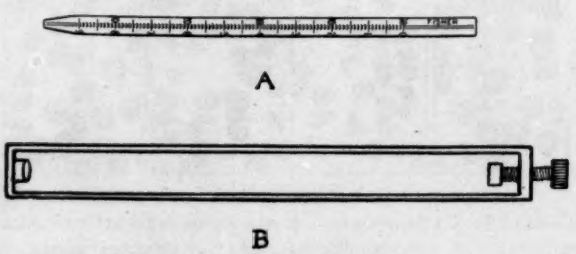


Fig. 3.—*A*, combination microhemopipet (Kato); *B*, metal holder with a rubber-cushioned metal cup at each end for sealing and immobilizing the pipet.

since the anticoagulant action of this mixture is slightly less than that of either heparin or liquoid when compared volume for volume. The anticoagulant solution so introduced is allowed to dry at room temperature. The slide is then taken to the patient's bedside, and from a moderately deep skin puncture 4 or 5 large drops (approximately 0.2 cc.) of freely flowing blood are received into the hollow of the slide. Then the blood and the anticoagulant are thoroughly mixed at once by means of a fine glass rod, great care being taken that the blood is rendered absolutely noncoagulable. The slide is then placed in a moist chamber and taken to the laboratory for the performance of the tests (fig. 2).

## SEDIMENTATION TEST

A clean dry combination micropipet (fig. 3) is filled to the top mark (50 cu. mm.) with the blood, which has first been completely homogenized by agitation. The two ends of the pipet are then closed by the rubber-cushioned cups of the

metal holder, and the pipet is set up in vertical position on the rack (fig. 4). The settling velocity of the red cell column may be recorded at any desired intervals during the sixty minutes of observation. The level reached in one hour's time is regarded as the sedimentation rate of the blood. Since the combination microhemopipet is graduated into 100 equal parts, the fall of the red cell column can easily be recorded in percentages. This is obviously a more rational way of recording the suspension stability of erythrocytes than the customary method of expressing it in terms of millimeters of fall, as practiced in the use of the majority of other instruments. The percentages will give accurate information as to the relations of the sedimentation of the red blood cells to the total volume of blood

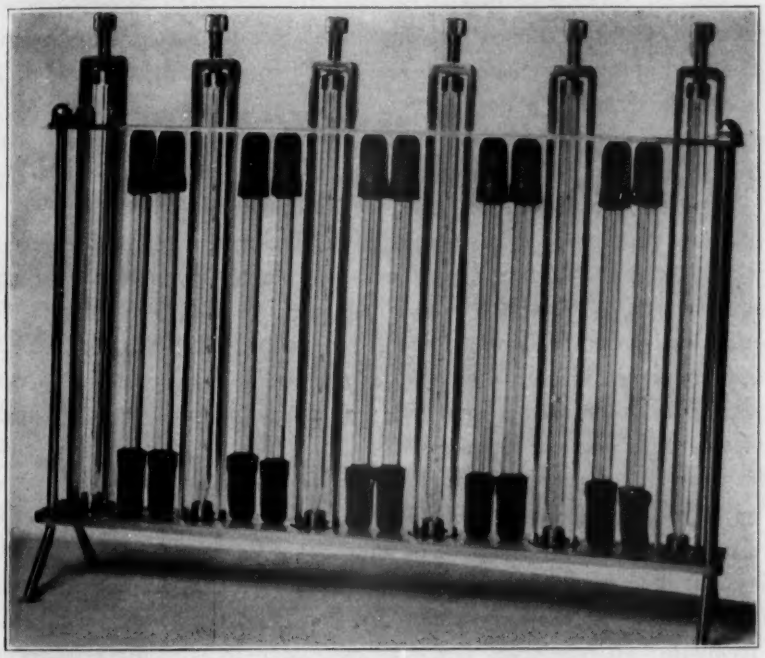

Fig. 4.—Special stainless steel rack provided with ten capillary tubes for the various concentrations of potassium dichromate solution used for determination of the icteric index and six combination microhemopipets, in metal holders, placed in vertical position for determination of the sedimentation rate.

used. Moreover, the percentage method of recording the sedimentation rate facilitates a ready and intelligent comparison with results obtained by other types of instruments.

## STANDARDS AND INTERPRETATION OF THE SEDIMENTATION RATE

In attempting to set up normal standards for the sedimentation rate certain mechanical factors necessarily involved in the use of the combination microhemopipet must be clearly appreciated. Since the instru-

ment is essentially a capillary pipet, the influence of the so-called action of capillarity on the rate of fall is theoretically unavoidable. But as a matter of fact most of the criticisms of the capillary method offered by certain observers (Walton;[12] Wintrobe and Landsberg[13]) are found to be due not so much to the capillary nature of the bore as to the improper choice of anticoagulants and to the lack of sufficient care in mixing the blood with the anticoagulant. With the use of heparin and liquoid in the proportions recommended the sedimentation test in a capillary pipet is found to be entirely satisfactory.

Although apparently independent of the anticoagulant used, sedimentation rates determined on samples of blood treated with heparin and liquoid appear to check with one another most satisfactorily, while samples mixed with oxalates give widely different results (figs. 5 and 6). For this reason the discussion of the suspension stability of erythrocytes is entirely confined to results obtained by the use of heparin and liquoid. The more significant data are presented in table 2.

In my experience low sedimentation rates were seen in cases of newborn infants (0 to 0.5 per cent), of polycythemia secondary to congenital heart disease (0.5 to 1 per cent) and of rheumatic heart disease with decompensation (0 to 2 per cent). High settling velocity was encountered in a case of aplastic anemia (82 per cent), in a case of acute lupus erythematosus (78 per cent) and in a case of acute leukemia with pronounced anemia (72 per cent). Moderately rapid rates were recorded in cases of rheumatic heart disease during the active stage (45 to 62 per cent) and of nutritional anemia with oligocythemia (32 to 47 per cent). In cases of nutritional anemia in which the red cell count is normal or relatively high (4,500,000 to 6,000,000 per cubic millimeter) the suspension stability is often low (fig. 7). Since anemia is frequently an important factor in increasing the rate of erythrocyte sedimentation, any attempt to correct the final record by means of so-called correction charts (Rourke and Ernstene;[14] Wintrobe and Landsberg[13]) is both unnecessary and misleading. The sedimentation rate should be simply recorded as actually observed, not as mutilated by artificial correction charts.

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12. Walton, A. C. R.: The Corrected Erythrocyte Sedimentation Test, J. Lab. & Clin. Med. **18**:711, 1933.

13. Wintrobe, M. M., and Landsberg, J. W.: Standardized Technique for Blood Sedimentation Test, Am. J. M. Sc. **189**:102, 1935.

14. Rourke, M. D., and Ernstene, A. C.: Method for Correcting Erythrocyte Sedimentations for Variations in Cell Volume Percentage of Blood, J. Clin. Investigation **8**:545, 1930.

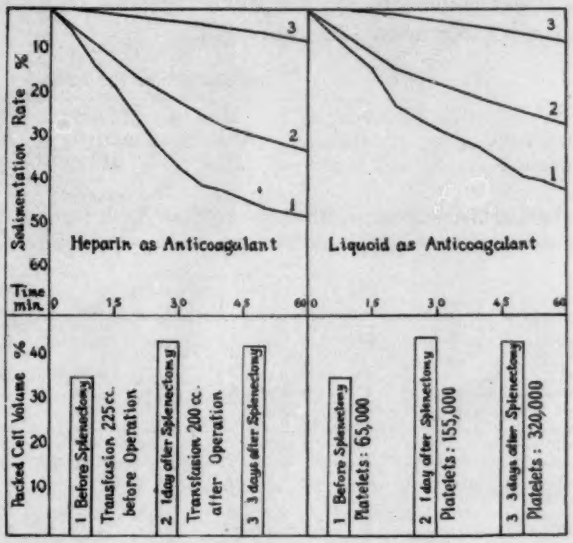


Fig. 5.—Influence of splenectomy on the sedimentation rate and the packed cell volume of a 5 year old infant with thrombocytopenic purpura. Heparin and liquoid were used in treating samples of blood obtained from one puncture in each of the 3 tests.

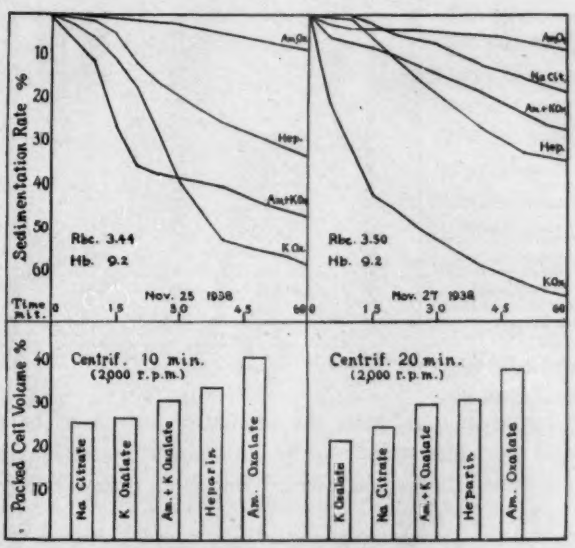


Fig. 6.—Effect of various anticoagulants on the sedimentation rate and the packed cell volume of a 6 month old infant with congenital syphilis.

While interpretation of the sedimentation rate cannot be fully set forth in a simple statement, yet the following scale of evaluation may be offered for consideration (see also fig. 8):

| Anticoagulant | Sedimentation Rates, % | | | |
|---|---|---|---|---|
| | Normal Range | Mild Activity | Moderate Activity | Severe Activity |
| Heparin | 0-20 | 21-40 | 41-60 | 61-100 |

TABLE 2.—*Typical Sedimentation Rates for Patients with Various Conditions**

| Diagnosis | Sex | Age | Sedimentation Rate, % in 1 Hour | Red Cells, Million | Packed Cell Volume, % | Hemoglobin, Gm. per 100 Cc. |
|---|---|---|---|---|---|---|
| Normal status | M | 1 mo. | 0 | 4.54 | 48 | 15.6 |
| Nutritional anemia | F | 18 mo. | 0 | 6.16 | 43 | 12.1 |
| Decompensation | M | 14 yr. | 0 | 5.66 | 50 | 16.0 |
| Normal status | M | 2 wk. | 0.5 | 5.02 | 54 | 19.2 |
| Nutritional anemia | M | 15 mo. | 0.3 | 6.76 | 35 | 9.5 |
| Chorea | M | 14 yr. | 1 | 4.68 | 37 | 12.0 |
| Decompensation | M | 8 yr. | 2 | 5.98 | 44 | 13.2 |
| Chorea | F | 13 yr. | 3 | 4.56 | 42 | 15.0 |
| Cyst of brain | F | 9 yr. | 4 | 5.64 | 30 | 11.4 |
| Infection of foot | F | 10 yr. | 5 | 4.90 | 37 | 15.1 |
| Ileostomy | F | 1 wk. | 7 | 3.63 | 37 | 13.4 |
| Sinusitis | F | 11 yr. | 9 | 5.24 | 40 | 13.7 |
| Nutritional anemia | M | 3 mo. | 11 | 3.42 | 32 | 11.0 |
| Nephrosis | M | 4 yr. | 11 | 4.39 | 37 | 10.7 |
| Chronic lung abscess | M | 5 yr. | 12 | 5.11 | 42 | 12.6 |
| Infectious mononucleosis | M | 10 yr. | 13 | 4.20 | 37 | 12.5 |
| Cleft palate with anemia | M | 6 mo. | 22 | 4.06 | 35 | 10.0 |
| Chorea (carditis ?) | M | 14 yr. | 25 | 6.09 | 45 | 13.5 |
| Hemiatrophy of face | M | 9 yr. | 32 | 5.50 | 39 | 12.8 |
| Purpura haemorrhagica | M | 5 yr. | 40 | 3.86 | 34 | 10.5 |
| Biliary obstruction | M | 6 mo. | 42 | 2.47 | 32 | 9.6 |
| Systemic thrush | F | 3 yr. | 44 | 5.24 | 34 | 13.0 |
| Neuroblastoma | F | 2 yr. | 45 | 1.90 | 21 | 6.5 |
| Congenital syphilis | F | 6 mo. | 45 | 4.36 | 33 | 9.4 |
| Nutritional anemia | M | 2 mo. | 46 | 3.60 | 34 | 10.2 |
| Rheumatic carditis | M | 14 yr. | 47 | 4.72 | 37 | 10.8 |
| Juvenile cirrhosis | F | 14 yr. | 50 | 3.92 | 40 | 17.2 |
| Cellulitis of neck | M | 2 mo. | 50 | 3.45 | 31 | 8.5 |
| Peritonitis, localized | F | 3 yr. | 50 | 4.40 | 31 | 9.3 |
| Scurvy with anemia | M | 20 mo. | 51 | 4.56 | 32 | 8.4 |
| Hemolytic jaundice | M | 13 yr. | 52 | 3.64 | 27 | 9.5 |
| Hemophilia | M | 13 yr. | 53 | 3.79 | 32 | 9.2 |
| Subdural hematoma | M | 4 mo. | 54 | 3.96 | 30 | 8.6 |
| Rheumatic carditis | M | 13 yr. | 57 | 4.00 | 32 | 10.4 |
| Idiopathic anemia | M | 2 wk. | 60 | 2.34 | 21 | 6.7 |
| Acute lupus erythematosus | F | 14 yr. | 66 | 3.50 | 27 | 8.8 |
| Acute leukemia | M | 14 yr. | 72 | 2.45 | 16 | 6.6 |
| Aplastic anemia | M | 9 yr. | 82 | 0.98 | 11 | 3.7 |

* Combination microhemopipet method.

It must be borne in mind that the tabulation is not to be used as an absolute scale for interpretation of any single determination of the sedimentation rate, since variations arising from many unknown factors frequently occur.

## PACKED CELL VOLUME

After the final reading of the sedimentation rate has been recorded, the pipet, without being removed from the metal holder in which it has been immobilized, is centrifuged for fifteen to twenty minutes at 2,000 revolutions per minute, or until no further diminution in the packed cell volume occurs. The results are again

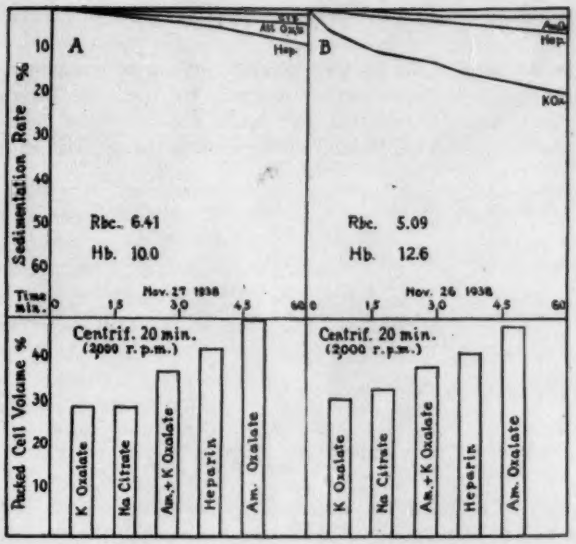


Fig. 7.—Influence of a high red cell count and packed cell volume on the sedimentation rate, *A*, of a 21 month old infant with nutritional anemia after otitis media, and *B*, of a 12 year old child with hematuria.

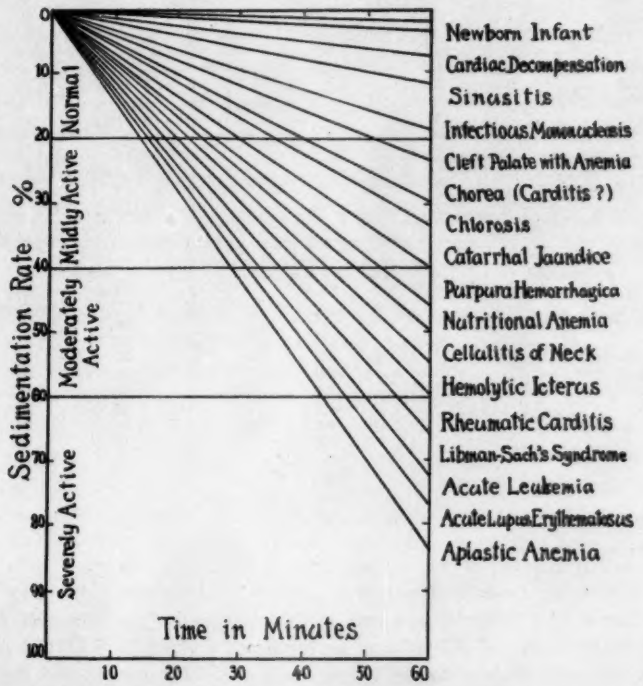


Fig. 8.—Typical sedimentation rates in certain pediatric conditions. The limits of normal sedimentation are 1 to 20 per cent, while higher percentage zones of 21 to 40, 41 to 60 and 61 to 100 per cent represent mild, moderate and severe activity, respectively.

recorded in percentages of the red cell volume. When anticoagulants other than heparin or the modified double oxalate mixture are used, the determinations of packed cell volume must be corrected with use of the correction factors suggested (table 3), as the hematocrit readings are influenced by the anticoagulants employed.

TABLE 3.—*Variations in Packed Cell Volume and Suggested Correction Factors with Heparin as Standard*

| Anticoagulant, Dry Form | Hematocrit Reading, % | Deviation from Heparin | Percentage of Deviation | Correction Factor, % |
|---|---|---|---|---|
| Heparin | 36.0 | 0 | 0 | 0 |
| Liquoid | 36.7 | +0.7 | 1.91 | — 2 |
| Ammonium oxalate | 42.3 | +6.3 | 14.89 | —15 |
| Double oxalate (Heller and Paul [5]) | 36.7 | —1.6 | 2.99 | + 3 |
| Sodium oxalate | 29.9 | —6.1 | 20.40 | +20 |
| Potassium oxalate | 28.6 | —7.4 | 25.87 | +25 |

TABLE 4.—*Scales of Icteric Index*

| Murphy (1926) | | Farahaugh and Medes (1929) | |
|---|---|---|---|
| Dilution of Dichromate | Icteric Index, Units | Dilution of Dichromate | Icteric Index, Units |
| 1:10,000 | 1 | 2:10,000 | 2 |
| 1:5,000 | 2 | 2.5:10,000 | 2.5 |
| 1:2,000 | 5 | 3:10,000 | 3 |
| 1:1,000 | 10 | 3.5:10,000 | 3.5 |
| 1:666 | 15 | 4:10,000 | 4 |
| 1:500 | 20 | 4.5:10,000 | 4.5 |
| 1:400 | 25 | 5:10,000 | 5 |
| 1:200 | 50 | 6:10,000 | 6 |
| 1:133 | 75 | 8:10,000 | 8 |
| 1:100 | 100 | 10:10,000 | 10 |

TABLE 5.—*Scales of Icteric Index According to Kolmer and Boerner*

| Dichromate Solution, 1:100, Cc. | Distilled Water, Cc. | Icteric Index, Units |
|---|---|---|
| 10.0 | 0 | 100 |
| 5.0 | 5.0 | 50 |
| 3.0 | 7.0 | 30 |
| 2.0 | 8.0 | 20 |
| 1.5 | 8.5 | 15 |
| 1.2 | 8.8 | 12 |
| 1.0 | 9.0 | 10 |
| 0.7 | 9.3 | 7 |
| 0.5 | 9.5 | 5 |
| 0.3 | 9.7 | 3 |
| 0.1 | 9.9 | 1 |

The topmost portion of the packed column is usually occupied by a grayish layer of leukocytes (usually 1 per cent), which in leukemic blood may be considerably increased. Recently, in a case of chloroleukemia in a 20 month old infant with a leukocyte count of 307,000 and an erythrocyte count of 1,520,000 per cubic millimeter, the packed erythrocyte volume was only 12 per cent, and the column was overlaid by a packed leukocyte column of 17 per cent, making a total of 29 per cent of all packed cells. Experience such as this indicates clearly the advisability, when dealing with leukemic blood, of recording the packed volumes of erythrocytes and leukocytes separately.

### ICTERIC INDEX

For estimation of the icteric index of the plasma a set of ten capillary tubes with bores of uniform diameter and identical with those of the pipets are mounted on a special rack (fig. 4). These capillary tubes are filled with aqueous solutions of potassium dichromate in concentrations corresponding to the scale of icteric index units recommended by either Murphy [15] or Farahaugh and Medes [16] (table 4). The various dilutions can be conveniently made from a stock dilution of 1:100 by the method suggested by Kolmer and Boerner [17] (table 5).[18]

The icteric index of normal plasma is less than 4 units; when the icteric index reaches 15 units or above, clinically observable jaundice is invariably present. In cases of severe icterus developing in the course of biliary obstruction, as well as in icterus gravis neonatorum and catarrhal jaundice, the icteric index may reach extremely high values (75 to 100 units).

### SUMMARY

The methods and standards for the determinations of the sedimentation rate, the packed cell volume and the icteric index by use of the newly devised combination microhemopipet are presented. Each individual series of these determinations was made from a single uniform small sample of capillary blood (50 cu.mm.) obtained by routine skin puncture. Since the entire procedure can be carried out simply and yet with relative accuracy, all these tests are strongly recommended for inclusion in routine examination of the blood. The information derived from these tests is especially essential to the accurate diagnosis and prognosis of anemias.

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15. Murphy, W. P.: Biliary System Function Tests, Arch. Int. Med. **37**:797 (June) 1926.

16. Farahaugh, C. C., and Medes, G.: A New Set of Potassium Dichromate Standards for Determination of the Icteric Index, J. Lab. & Clin. Med. **14**:681, 1929.

17. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, ed. 2, New York, D. Appleton-Century Company, Inc., 1938, p. 234.

18. The use of blue glass with a wavelength of approximately 4,400 angstrom units will make the minute gradations of yellow color distinct and sharp.

# SMALLPOX VACCINATION OF NEWBORN INFANTS WITH CULTURE VIRUS AND WITH CALF LYMPH VIRUS

## A COMPARATIVE STUDY OF INTRADERMAL AND CUTANEOUS VACCINATION WITH THE TWO VIRUSES IN OVER A THOUSAND INFANTS

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It is generally admitted that smallpox vaccination should be done for the first time in early infancy; the choice of age varies from the third month to the end of the first year. "In 1936, of the more than 2,000,000 live births, nearly 900,000, or two fifths, took place in hospitals. Nearly three quarters of the births in cities were in hospitals, as compared with one seventh in rural areas." [1] Healthy full term babies may be vaccinated the day of their birth with practically no risk at all.[2] Among the poor there is no time so opportune for vaccination as at birth in the maternity hospital. Two or three subsequent vaccinations by the age of 30 years would meet Topley's recommendations [3] for the substantial elimination of the disease, except in epidemic times, during which he advocated "the immediate vaccination or revaccination of all contacts, and of the largest number of those living in the community at risk."

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The work reported here was made possible in part through a grant in aid by the National Research Council.

From the Department of Pediatrics, George Washington University School of Medicine, the Gallinger Municipal Hospital, and the Allergy Clinic of Children's Hospital.

1. Proceedings of Conference on Better Care for Mothers and Babies Held in Washington, D. C., Jan. 17-18, 1938, Bureau Publication 246, United States Department of Labor, Children's Bureau, 1938, p. 33.

2. Donnally, H. H., and Nicholson, M. M.: A Study of Vaccination in Five Hundred Newborn Infants, J. A. M. A. **103**:1269 (Oct. 27) 1934.

3. Topley, W. W. C.: An Outline of Immunity, Baltimore, William Wood & Company, 1933.

For infants under the care of private physicians who practice preventive pediatrics, vaccination may come after the neonatal period, but vaccination is as a rule advisable for infants before they reach 6 months of age.

Among research workers in the vaccinia field, a solution to the problem of establishing immunity to smallpox without severe cutaneous lesions, with vaccinia virus free of bacteria and other viruses, has been widely sought. The object of this is to bring about protection with as little discomfort as possible and without bacterial invasion. Yet the reaction of individual patients is variable and unpredictable; the same dose of the same material at the same time may give a very slight reaction in one baby and a more extensive reaction in another (fig. 1). While this is true, it is also true that with the best virus available, the

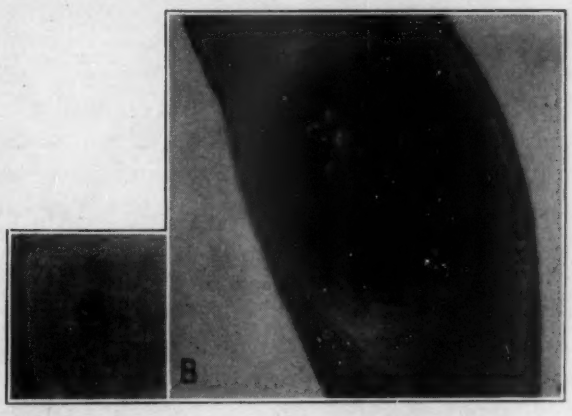


Fig. 1.—Peak of cutaneous reactions obtained with culture virus (Rivers) on the ninth day. *A*, reaction in one infant; *B*, reaction in another infant.

reactions resulting in the great majority of babies will be mild, and severe reactions, decidedly exceptional.

Rivers,[4] who worked on the problem of mildness but sufficiency of reaction to vaccine virus, offered a twofold answer: first, his culture virus, and second, intradermal[5] inoculation with it. Our study of vaccination of newborn infants has included the inoculation of over

4. (*a*) Rivers, T. M.: Cultivation of Vaccine Virus for Jennerian Prophylaxis in Man, J. Exper. Med. **54**:453 (Oct.) 1931. (*b*) Rivers, T. M., and Ward, S. M.: Further Observations on the Cultivation of Vaccine Virus for Jennerian Prophylaxis in Man, ibid. **58**:635 (Nov.) 1933; (*c*) Jennerian Prophylaxis by Means of Intradermal Injections of Culture Vaccine Virus, ibid. **62**:549 (Oct.) 1935.

5. Roberts, B. E.: Subcutaneous and Intradermal Smallpox Vaccination, J. Prev. Med. **6**:453 (Nov.) 1932. Toomey, J. A., and Hauver, R. B.: Intradermal Vaccination, Am. J. Dis. Child. **35**:186 (Feb.) 1928.

500 newborn infants with culture virus (Rivers) by the intradermal method. This group was compared with a group of 313 newborn infants inoculated intradermally with diluted calf lymph. Rivers also devised a culture virus for the cutaneous method[4c] of vaccinating. In our study there are reported the reactions of 128 infants given cutaneous inoculations with this material, and comparison is made with the reactions of 134 infants in a control group given cutaneous inoculation with undiluted glycerolated calf lymph treated with brilliant green (obtained from the Bureau of Laboratories of the city of New York), an admirable and potent calf lymph virus.

### WHAT CONSTITUTES A "TAKE"

We have given a great deal of attention to the cutaneous reactions in the different groups already mentioned. It would appear that there is a lower limit beyond which one may not go in regarding the local reaction as a "take." How is one to tell whether a very small cutaneous reaction should be accepted as a "take?" We are unable to answer this question, although we realize that if the infection "takes" at all, we have good reason to believe that the vaccinia virus always becomes generalized and that the size of the cutaneous reaction is probably of little importance so long as it occurs as a definite vaccinal cycle.[6]

### AUTHORS' PREVIOUS REPORT

Two of us (H. H. D. and M. M. N.) recently reported on the vaccination of 500 newborn infants.[2] In that study, glycerolated calf lymph (undiluted) from a commercial biologic laboratory was used. Leake's multiple pressure method[7] of cutaneous vaccination was employed, with thirty pressures of the needle and severe trauma of the skin at the site, accomplished by rubbing in the lymph virus in various directions with the needle held flat against the skin. Successful inoculation of 90 per cent of 289 consecutive babies resulted. A little more than 10 per cent of the "takes" had vesicles 20 mm. and more in diameter and large areolas. Six babies successfully vaccinated at birth or the following week were revaccinated at 4 to 7 weeks of age with the severest technic. Successes in only 2 of them resulted, while a control group of 9 babies of the same age, not successfully vaccinated at birth, all had vesicles from 15 to 20 mm. in diameter. A group of 52 babies

6. Craigie, cited by Tulloch, W. J.: The Harben Lectures, 1934: Serological Diagnosis of Smallpox and Laboratory Investigation of Vaccinia, J. State Med. **42**:683 (Dec.) 1934.

7. Leake, J. P.: Questions and Answers on Smallpox and Vaccination, Pub. Health Rep. **42**:221 (Jan. 28) 1927.

successfully inoculated at birth were revaccinated at the age of 13 to 16 months; "takes" resulted in 30.8 per cent of the babies vaccinated; in 69.2 per cent, immune reactions occurred. Similar figures for "takes" and immunity on revaccination have been reported at all ages.[8]

### INTRADERMAL VACCINATION OF NEWBORN INFANTS

*Method Used.*—With a 26 gage needle and a tuberculin syringe, 0.1 cc. of culture virus (Rivers) or diluted calf lymph was injected into the skin cleansed with 95 per cent alcohol, after the manner used in the Mantoux, Schick and Dick tests (fig. 2), producing a bleb dimpled by the follicles. As the needle was withdrawn, the site was swabbed freely with 95 per cent alcohol to kill any virus escaping along the needle track.[4c]

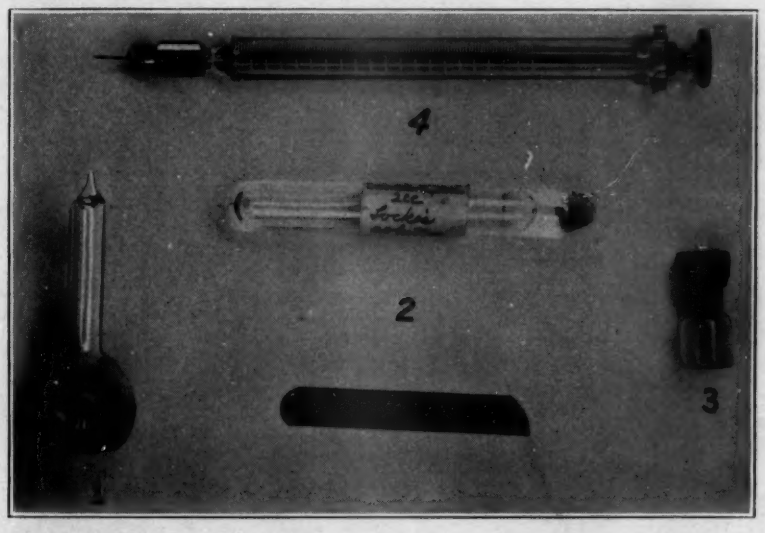


Fig. 2.—Materials and syringe for intradermal smallpox vaccination, with culture virus (Rivers) or with diluted calf lymph virus. *1*, culture virus (Rivers); (*2*), Locke's solution, 2 cc.; *3*, calf lymph virus from the New York City Bureau of Laboratories; *4*, tuberculin syringe; the fifth object (not numbered) is a file.

*Culture Viruses Used.*—Culture virus desiccated at low temperatures in the presence of acacia [4c] was supplied to us by Dr. Rivers in pyrex glass ampules. Two cubic centimeters of Locke's solution and later physiologic (0.85 per cent) solution of sodium chloride was added to the ampule, and when mixed the solution was taken up in the tuberculin syringe and injected intradermally, as described. The Bureau of Laboratories, New York, supplied us with ripened glycerolated calf lymph virus to which brilliant green had been added. Assistant director Charles R. Tyler sent a supply from time to time in rubber-capped vials.

8. Sergent, A., and Trensz, F.: De la perte d'immunité vaccinale, Bull. Acad de méd., Paris **107**:625 (May 3) 1932.

*Course of the Reactions to Culture Virus and to Calf Lymph.*—In two thirds of the newborn infants vaccinated intradermally (figs. 3 and 4) with culture virus after a period of latency or incubation, the cutaneous reaction appeared on the fourth, and fifth or the sixth day after the inoculation. The lesion appeared as a red macule, a red nodule, or a small vesicle with a red rim. The papilla and the surrounding redness gradually increased for the next five or six days; generally the vesicle became umbilicated. About the tenth or the twelfth day there was a rapid increase in the area of redness about the lesion, with infiltration

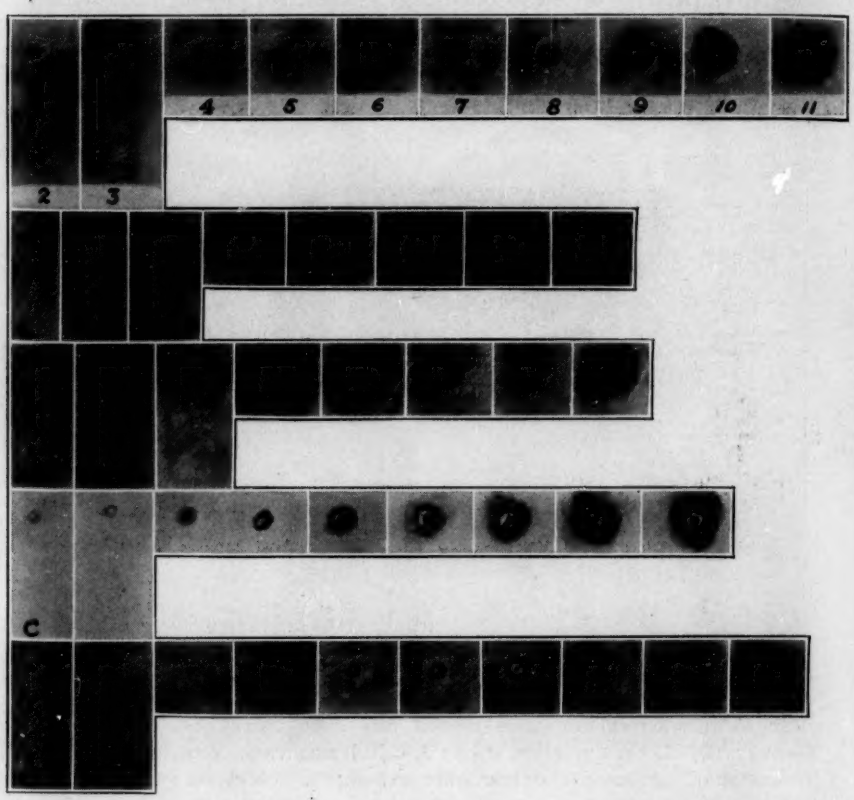


Fig. 3.—Primary vaccinal cycle in newborn infants resulting from intradermal vaccination with culture virus (Rivers). Figures show the age of reaction in days after inoculation; *c* shows the site of control inoculation with unseeded mediums.

of the subcutaneous tissue for a day; then the whole cutaneous reaction underwent resolution. In 82.25 per cent of the reactions there was regional lymphadenopathy (table 1). Vesicles were present in 70.75 per cent, and ruptured vesicles with crusts in 27 per cent; most of these vesicles were small and superficial. The maximum size of the papillae (table 2) did not exceed 4 mm. in diameter in 44.5 per cent, with 44.2 per cent measuring 5 to 9 mm., making a total of 89 per cent with papillae 9 mm. or less in diameter. In the reactions of half the babies, the redness (table 3) did not exceed 10 mm., and in 95 per cent, it did not exceed

30 mm. In the reactions of the remaining 5 per cent of the babies, maximum redness exceeded 50 mm. in 0.75 per cent of the babies vaccinated. In 25 of the babies, we employed inoculation of the mediums unseeded with vaccinia virus but otherwise handled and inoculated in exactly the same way. These sites are marked *C* in the drawings. The slight evidence of cutaneous trauma lasted a day or two and disappeared. Thus 90 to 95 per cent of the newborn infants vaccinated intradermally with culture virus (Rivers) had mild cutaneous lesions. The lymphadenopathy in 80.25 per cent of the reactions indicated invasion of the body by the virus.

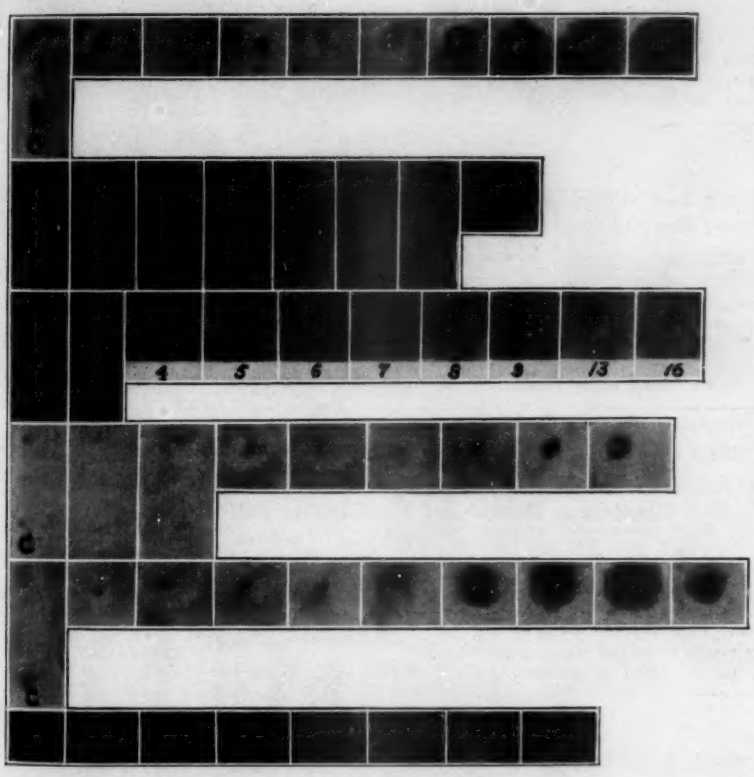


Fig. 4.—Primary vaccinal cycle in newborn infants resulting from intradermal vaccination with culture virus (Rivers). Figures show the age of reaction in days after inoculation; *c* shows the site of control inoculation with unseeded medium.

Calf lymph virus, 1 part in 100 of saline solution (0.1 cc. inoculated intradermally), brought 93 per cent of "takes." Comparing the cutaneous lesions (fig. 5) resulting from intradermal vaccination with culture virus (Rivers) and calf lymph virus (New York City Bureau of Laboratories) in 1 to 100 dilution, the reactions were essentially similar, almost identical, in newborn infants with "takes." In the calf lymph series (table 1) vesicles occurred in 84 per cent of the reactions, as compared with 71 per cent of the reactions with culture virus. Lymphaden-

opathy was present in about 89 per cent of the reactions in the calf lymph series, in contrast to 82 per cent of the reactions in the culture virus series. A striking difference between the reactions to the two viruses (fig. 6) was the shorter incubation period for the calf lymph virus, 35 per cent of the cutaneous reactions appear-

TABLE 1.—*Comparison of the Cutaneous Reactions to Culture Virus and to Calf Lymph in the Intradermal Inoculation of Newborn Infants*

| Type of Virus | Percentage Showing Vesicle | Percentage Showing Rupture of Vesicle | Percentage Showing Adenopathy |
|---|---|---|---|
| Culture virus (Rivers) 400 infants | 70.75 | 27.0 | 82.25 |
| Calf lymph 1:100 (brilliant green) (N. Y. C. Bu. Lab.) 290 infants | 84.1 | 24.8 | 88.6 |

TABLE 2.—*Comparison of the Maximum Size of the Papillae in Reactions to Culture virus and the Calf Lymph in the Intradermal Inoculation of Newborn Infants*

| Type of Virus | 4 Mm. or Less | 5 to 9 Mm. | 10 to 19 Mm. | 20 Mm. or Over |
|---|---|---|---|---|
| Culture virus (Rivers) 399 infants | 44.5% | 44.2% | 10.0% | 1% |
| Calf lymph 1:100 (brilliant green) (N. Y. C. Bu. Lab.) 289 infants | 44.8% | 47.2% | 7.0% | 0 |

TABLE 3.—*Comparison of the Maximum Redness Surrounding the Papillae in Reactions to Culture and Virus and to Calf Lymph in the Intradermal Inoculation of Newborn Infants*

| Type of Virus | 10 Mm. or Less | 11 to 30 Mm. | 30 to 50 Mm. | Over 50 Mm. |
|---|---|---|---|---|
| Culture virus (Rivers) 400 infants | 49.0% | 45.7% | 4.25% | 0.75% |
| Calf lymph 1:100 (brilliant green) (N. Y. C. Bu. Lab.) 290 infants | 47.3% | 45.1% | 6.9% | 0.3% |

TABLE 4.—*Comparison of the Successful Reactions to Culture Virus and to Calf Lymph in the Intradermal Inoculation of Newborn Infants*

| Type of Virus Used | Number of Infants Vaccinated | Number Successful | Percentage Successful |
|---|---|---|---|
| Culture virus (Rivers) | 515 | 400 | 77.6 |
| Calf lymph 1:100 (brilliant green) (N. Y. C. Bu. Lab.) | 313 | 290 | 92.7 |

ing on the third day, in contrast to 5 per cent for the culture virus; the cutaneous reactions appeared on the fourth, the fifth or the sixth day in a large portion of the remaining babies vaccinated with each virus.

When the "takes" in the two groups (table 4) are considered together, 515 newborn infants receiving intradermal vaccinations with culture virus (Rivers)

yielded 400, or 77.7 per cent successes, while among 313 newborn infants vaccinated intradermally with calf lymph virus (diluted 1 to 100), 290, or 93 per cent, of the vaccinations were successful.

## CUTANEOUS VACCINATION OF NEWBORN INFANTS

For cutaneous vaccination Dr. Rivers supplied us with a culture virus consisting of 3 parts of virus mixed with 1 part of sterile egg albumin [4c] desiccated in 0.25 cc. amounts inside small test tubes, which had been sealed off. This virus

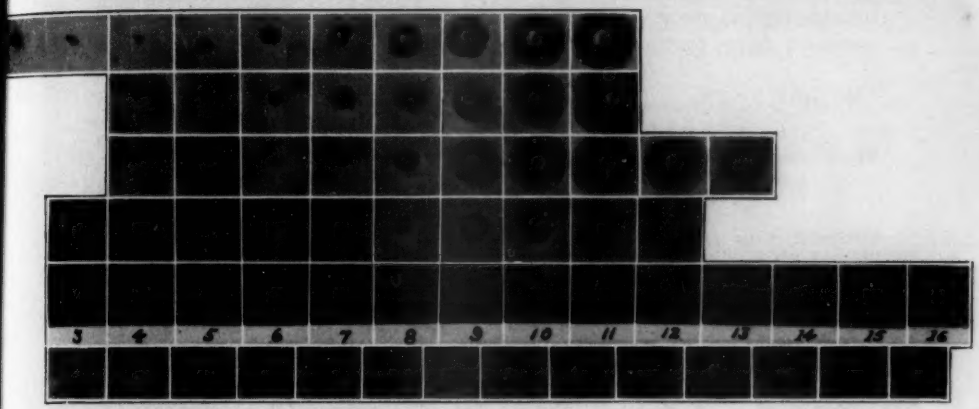


Fig. 5.—Primary vaccinal cycle in newborn infants resulting from intradermal vaccination with diluted calf lymph virus from the New York City Bureau of Laboratories. Figures show the age of the skin lesion in days after inoculation.

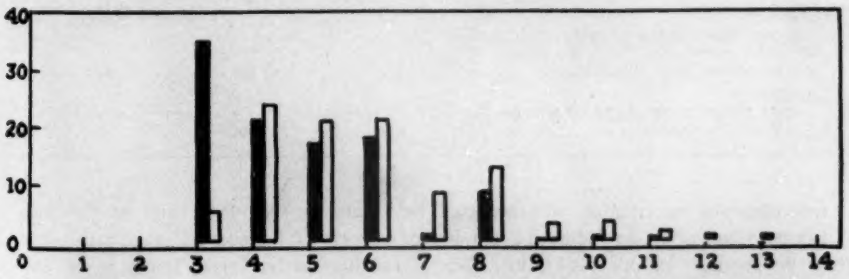


Fig. 6.—Comparison of the incubation periods of vaccinations with culture virus and calf lymph virus. The days required for incubation are indicated in percentage for the culture virus by vertical outlines in black and for the ~~culture~~ lymph virus by vertical solids in black.

was prepared for use by opening the test tubes aseptically, pulverizing the virus and transferring it with a sterile wooden applicator to cutaneous scratches; it was then gently rubbed in. In the 128 newborn infants vaccinated by scratching the skin with a needle and rubbing the pulverized culture virus mixed with egg white into the skin, there were 13 "takes," or 10 per cent of successes (table 5). In the control group, vaccinated cutaneously with glycerolated calf lymph (undiluted), there were 125 "takes," or 93.3 per cent of successes, among the 134 newborn infants so inoculated.

### INTRADERMAL COMPARED WITH CUTANEOUS VACCINATION

Mention has been made [2] of the difficulty in securing "takes" among newborn infants by cutaneous vaccination with undiluted calf lymph and of the considerable trauma employed in order to obtain successes. The result was that over 10 per cent of the "takes" of these vaccinations were too severe, causing vesicles 20 mm. in diameter, and large areolas. This reaction contrasted greatly with the insignificant trauma accompanying intradermal vaccination with calf lymph diluted 1 to 100. Yet the percentage of successes among the two groups of newborn infants vaccinated by the two methods was almost identical; in 134 babies in the cutaneously inoculated group there were 125 successes, 93.3 per cent, while the intradermally inoculated group, containing 313 babies, had 290 successes, 92.7 per cent (table 6).

TABLE 5.—*Comparison of the Successful Reactions to Culture Virus and to Calf Lymph in the Cutaneous Inoculation of Newborn Infants*

| | Newborn Infants | Successful | Percentage Successful |
|---|---|---|---|
| Cultivated virus (Rivers) (1 part egg-white, 3 parts culture virus glycerolated, 50%) | 128 | 13 | 10.0 |
| Calf lymph virus glycerolated, undiluted (N. Y. C. Bu. Lab.) (brilliant green) | 134 | 125 | 93.3 |

TABLE 6.—*Comparison of the Successful Intradermal Vaccinations with the Successful Cutaneous Vaccinations*

| Method | Number of Infants | Number Successful | Percentage Successful |
|---|---|---|---|
| Cutaneous | | | |
| Glycerolated undiluted calf lymph (brilliant green) (N. Y. C. Bu. Lab.) 30 pressures plus rubbing | 134 | 125 | 93.3 |
| Intradermal | | | |
| Calf lymph 1:100 (brilliant green) (N. Y. C. Bu. Lab.) | 313 | 290 | 92.7 |

Subcutaneous vaccination was reported by Chauveau [9] in 1865, and in the past twenty years or so an increasing number of reports of intradermal vaccination are to be found.[5] In our study, intradermal vaccination has been found to be far superior to the cutaneous method as used in both groups of babies, those inoculated with culture virus and those vaccinated with diluted calf lymph. The culture virus had been proved to be free of bacteria and other viruses; it as well as the diluted calf lymph used in this study resulted in no recognized infections among the babies inoculated intradermally, while cutaneous reactions caused by the two inoculums were practically identical—facts which have already been mentioned. Less than 1 per cent of the "takes" caused vesicles over 20 mm. in diameter; when the two groups of intradermal vaccinations are combined, it is found that 400 culture virus "takes" caused 4 reactions with vesicles as great as 20 mm. in diameter, or 1 per cent, and that 290 "takes" among the calf lymph group caused no vesicles as great as 20 mm. in diameter.

9. Chauveau, M.: Bull. Acad. de méd., Paris **31**:1111, 1865-1866; cited by Roberts.[5]

## CONCLUSIONS

Cutaneous and intradermal vaccination of newborn infants with calf lymph virus from the New York City Bureau of Laboratories, undiluted and diluted 1 : 100, respectively, yielded the same percentage of "takes," 93 per cent.

The percentage of successful "takes" in newborn infants vaccinated intradermally with culture virus (Rivers) was somewhat lower, approximately 80 per cent.

Cutaneous vaccination with culture virus mixed with sterile egg white, desiccated and rubbed into the skin scratches yielded "takes" in only 10 per cent of newborn infants. Its use therefore is not recommended.

The cutaneous reaction and the invasiveness of the virus, indicated by the lymphadenopathy, are practically identical with the culture virus and the diluted calf lymph when both are used intradermally.

Minimal cutaneous trauma accompanied intradermal vaccination.

Bacterial infection was apparently absent.

The intradermal use of culture virus and of calf lymph diluted 1 : 100 generally yielded mild cutaneous lesions in newborn infants. Unexpectedly marked cutaneous reactions occasionally occurred with the use of both viruses. Likewise, mild cutaneous reactions with both viruses at times left doubt as to whether they should be regarded as "takes." Lymphadenopathy present in over 80 per cent of the babies favored the interpretation of the inoculation as successful.

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# STABILIZATION OF THE DIABETIC CHILD

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The difficulties encountered in treating diabetes mellitus in the child or the young adult are so numerous that often the disease is inadequately managed. The disadvantages of incomplete control are not immediately apparent, but it is unreasonable to think that a poorly controlled patient will do as well as one whose metabolism is as nearly normal as treatment will permit.[1] This report deals with a regimen of control which is designed to approximate normal conditions of metabolism and with the typical response of children who have been treated in accordance with that regimen.

Of a group of 131 diabetic children under active management, 53 have been studied for an aggregate of more than three thousand days in the hospital during the past three years. Each of these responded to treatment in a similar manner. The records of 27 of these patients were found especially adaptable to statistical analysis because they showed freedom from complicating factors. From these records the average response has been determined.

## REGIMEN

The regimen employed was constant in all essentials. Competent dietetic personnel was responsible for calculation of diets, weight and preparation of food and supervision of its ingestion. All urine voided was analyzed by competent and constant personnel, who also determined the blood sugar levels of the patients at intervals throughout the twenty-four hours several days each week. Constant maintenance of specially trained nursing personnel made for accuracy in dosage of insulin, site and depth of injection, standardization of exercise, collection of specimens of urine, treatment of insulin shock and recording of any variable factors which arose during the period of study. Basically the method of management was similar to that previously described by one of us.[2]

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From the Department of Pediatrics, State University of Iowa.

1. Boyd, J. D., and Jackson, R. L.: Levels of Control in the Treatment of Diabetes Mellitus, J. A. M. A. **111**:906 (Sept. 3) 1938.

2. Boyd, J. D., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 3, chap. 12.

The diets were designed to meet fully each patient's needs according to modern nutritional knowledge. The child's height and his theoretic weight as calculated from his height and age were used as guides in determining the requirements for a diet which would allow a gram or more of protein for each pound of theoretic weight, calories for full activity and a constant ratio of protein, carbohydrate and fat. The fatty acid to dextrose ratio (by weight) was 1 to 1½. Three equal meals

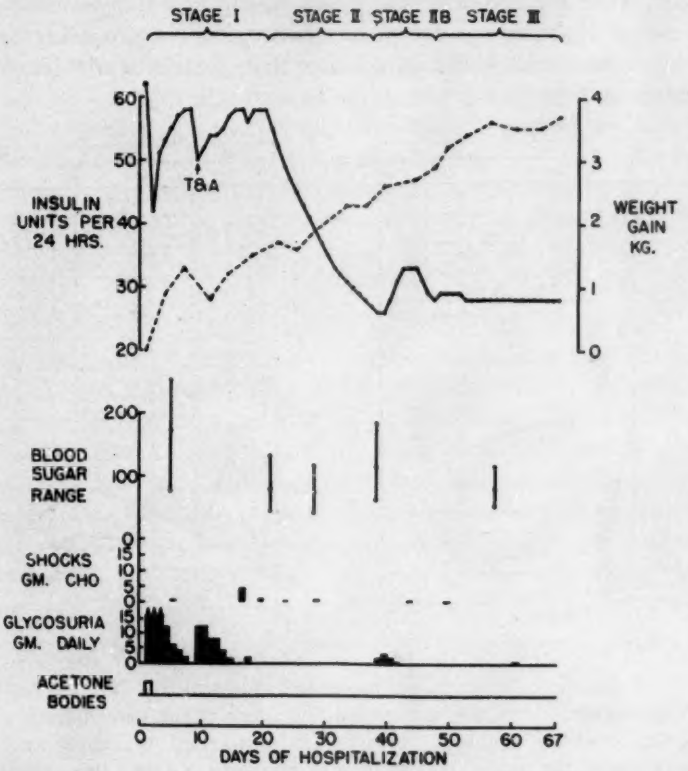


Chart 1.—The average response of 27 diabetic children to the regimen of control. The heavy line represents daily dosage of insulin; the broken line, gain in weight. *T & A* indicates the time of removal of tonsils and adenoids. The blood sugar ranges charted represent the mean maximum and minimum and the average values for the group.

were given, at 7 a. m., 12 noon and 5 p. m. Regular insulin was used, the total dosage for each patient being determined by the trial and error method. The initial dosage was gaged from the degree of glycosuria, the available dextrose in the diet and the age and height of the child; it usually ranged from 20 to 100 units in each twenty-four hours, of which 35 per cent was given a half-hour before breakfast, 22 per cent

a half-hour before the noon meal, 28 per cent a half-hour before the evening meal and the remaining 15 per cent at midnight.

Care was taken to detect insulin shocks early and to avoid overtreating them. Frequently it was possible to use some part of the next meal as an antidote, such as half a glass of milk. Otherwise, ½ to 1 ounce (15 to 30 cc.) of orange juice was given. This treatment was not repeated unless necessary, and then not until five or ten minutes had elapsed. Profound shocks were seldom encountered in this group of children; when they occurred the policy was to give intravenously 20 to 50 cc. of a 5 per cent solution of dextrose. This procedure hastens recovery and obviates the possibility that gastric stasis may delay absorption.

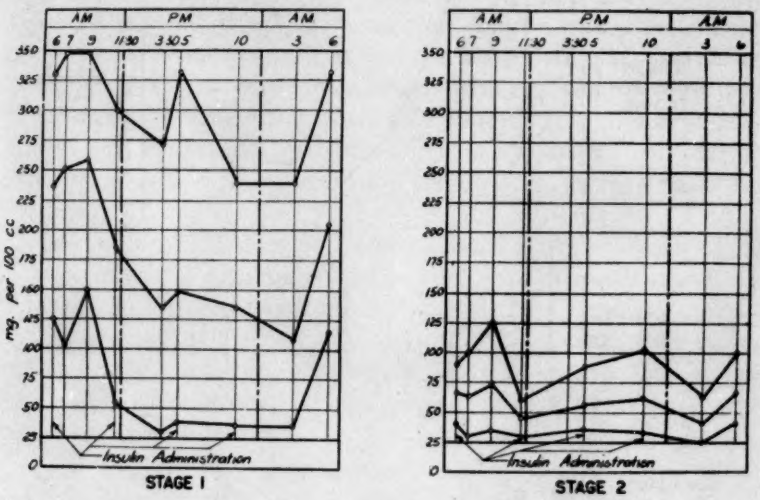


Chart 2.—The curves at the left represent the diurnal fluctuations in blood sugar of 27 diabetic children during the period of glycosuria. The curves on the right represent the diurnal fluctuations in blood sugar of the same diabetic patients during the period of metabolic recovery. In each chart the upper and lower curves represent the single maximum and minimum values; the center curve represents the average of all diurnal determinations.

In addition to laboratory studies and supervision of diet and of administration of insulin, the hospital regimen of these children provided for control of their physical activities.

## PHASES OF STABILIZATION

*Stage 1.*—Chart 1 shows the typical response of the patients to this regimen throughout their entire stay in the hospital. Initial ketosis was treated by intravenous administration of isotonic solution of dextrose or of Ringer's solution or of both and by the concurrent injection of

insulin in amounts sufficient to cause the disappearance of acetoacetic acid from the urine. When the patient was free from complications, he was placed under the regimen of diet and insulin described in the foregoing paragraphs, the insulin dosage being adjusted daily to overcome glycosuria. It was planned to remove or to treat suitably any active or potential foci of infection as early in the course of treatment as possible. Operative intervention was undertaken as soon as the patient was hydrated, gaining weight and excreting only small amounts of sugar in the urine.

For this group of patients an average of eighteen days was required to complete the phase of control which has been described; included in this period is an average time of seven and a half days required after tonsillectomy to regain the preoperative diabetic status. In chart 1 this period is indicated as stage 1; it is characterized by rapid clinical improvement. By the end of this stage the patient had become subjectively well and was gaining weight. Minimal glycosuria was present, and the patient was receiving much more insulin than the ultimate requirement.

The diurnal blood sugar values, as seen in chart 2, fluctuated widely during this stage and most of the time were above normal. In our earlier studies many patients were permitted to leave the hospital at this period of treatment, because of the belief that the function of the hospital had been fulfilled. Mild glycosuria was not uncommon, but the parents had been told to complete the establishment of insulin dosage at home, with urine tests as a guide. Subsequent studies of these children have indicated that they were not successfully stabilized at home and that they failed to show the improvement which will be described as characteristic of the more prolonged period of hospital control. The majority of children under diabetic management in the country at large remain in this stage of inadequate control.

*Stage 2.*—However, this study indicates that if the patient continues with his hospital regimen and the insulin dosage is kept at a level which avoids both glycosuria and severe insulin shock, the exogenous insulin requirement decreases rapidly. This period of decrease in insulin requirement represents a period of metabolic recovery during which the sugar-handling function is restored in a noteworthy degree. In the charts this period is designated as stage 2. The child needs most careful supervision during this period. Unless foresight in prescribing insulin is used, the aglycosuria is followed by insulin shock. This may be overtreated either because of alarm at the manifestations of shock or because of an overestimation of the amount of sugar needed for its correction. Overtreatment leads to recurrence of glycosuria, and if its cause is not recognized the dosage of insulin may be raised to correct it. The patient

so treated will fluctuate between glycosuria and insulin shock, and the physician or parent accepts mild glycosuria as less of a menace than repeated insulin reaction. The maintenance of minimal glycosuria prevents the reduction of insulin dosage which characterizes the period of metabolic recovery.

On the other hand, correct treatment permits maximum recovery of the sugar-handling mechanism and a final stabilization with an insulin requirement averaging approximately half of the dosage at the end of stage 1. This reduction of the earlier requirement ranged from two thirds for the younger patients who had been diabetic only a short time to one third for the older children with protracted diabetes.

The present plan of treatment for stage 2, based on the data obtained from the 27 patients, is as follows: As soon as the child has been aglycosuric for twenty-four hours, the insulin dosage is reduced by an amount equal to about 5 per cent of the total insulin requirement for the previous day. For example, a patient receiving 58 units of insulin in twenty-four hours (20 units before the morning meal, 13 units before the noon meal, 16 units before the evening meal and 9 units at midnight) would receive 55 units the following day (19, 12, 16 and 8 units, respectively). The next day the patient would receive 52 or 53 units in the same percentage and time distribution. This daily diminution of dosage continues until glycosuria recurs or aglycosuria can be maintained without insulin shocks. The diurnal values for blood sugar should remain approximately within the normal range. It is rarely possible to prevent insulin shocks during this period; with the described method of decreasing dosage, however, these shocks should be minimal and usually will respond to ½ or 1 ounce (15 to 30 cc.) of orange juice. Aglycosuria cannot be maintained if shocks are overtreated or if the insulin dosage is reduced at a more rapid rate than that for which the rate of spontaneous recovery can compensate.

*Stage 2 B.*—The average duration of the stage of metabolic recovery was approximately sixteen days. During this period, as indicated in chart 2, the diurnal values for blood sugar remained within a relatively narrow range and frequently were below the normal level. It will be noted that the insulin requirement became relatively constant toward the termination of stage 2; the dosage often was reduced below the level of the patient's needs at that time, resulting in higher and more widely fluctuating blood sugar values and frequently in glycosuria. This is a period of transition (stage 2 B) between the stage of metabolic recovery and the terminal stage of true stability (stage 3) and required an average of nine and a half days.

*Stage 3.*—The period of stability was not reached until the patient had been under careful management for several weeks, in this series an

average of thirty-five days. During this time aglycosuria and relatively normal blood sugar levels had been maintained in so far as possible. Once the patient had reached stability the insulin requirement for the maintenance of desirable blood sugar levels was practically constant, glycosuria had ceased and insulin shocks were no longer noteworthy. Values for blood sugar no longer showed the degree of oscillation that characterized the earlier stage of management and approximated the normal level. The constancy of this stage has been established in our patients by continued hospital observation during approximately three weeks after the completion of the second stage of management. Once such stability had been reached these patients proved excellent subjects for studying variations in therapeutic tech-

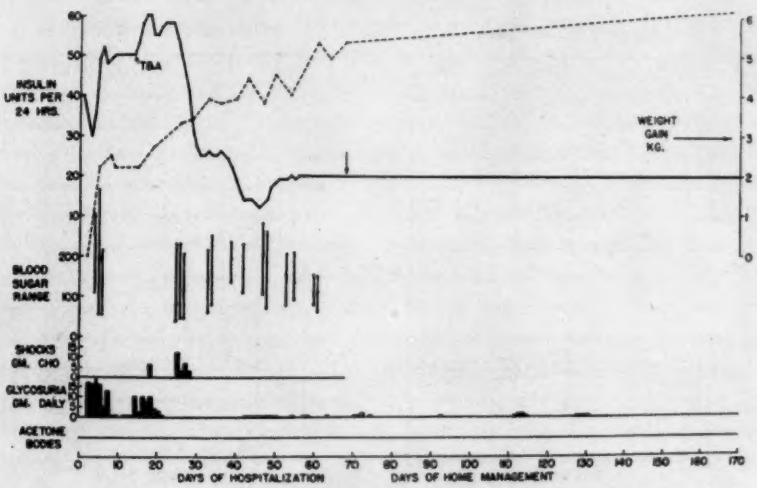


Chart 3.—A record of the response of an 11 year old girl with diabetes of recent onset. The arrow indicates the time at which the patient was released from the hospital. The symbols are those used in chart 1. There were no insulin shocks during the period of home management. The blood sugar values indicate the maximum, minimum and average of eight determinations for each day indicated.

nic. It appears obvious that unless stability has first been established one cannot safely draw conclusions from differences in response to various regimens. Chart 3 shows the response of an individual patient to this regimen of control in the hospital and the subsequent maintenance of stability under home management.

## COMMENT

As has been emphasized, the stabilization of these patients was accomplished through detailed laboratory studies, including quantitative determinations of urinary sugar and frequent determinations of blood

sugar. Using the typical response of the children in this group, we have been able recently to regulate patients through the first two stages of management by the use of qualitative urinalyses and by the occurrence of mild shocks, dispensing with determinations of blood sugar during this phase of management. During the latter part of the period of metabolic recovery, however, studies of the blood sugar shortened the time required for stabilization and the period of hospitalization. Trial and error may suffice for the establishment of stability, provided the terminal period is characterized by normal blood sugar values. Since the success in further treatment rests so largely on the attainment of true stability, it is desirable to use blood sugar content as a guide whenever possible, especially before the patient is finally dismissed from

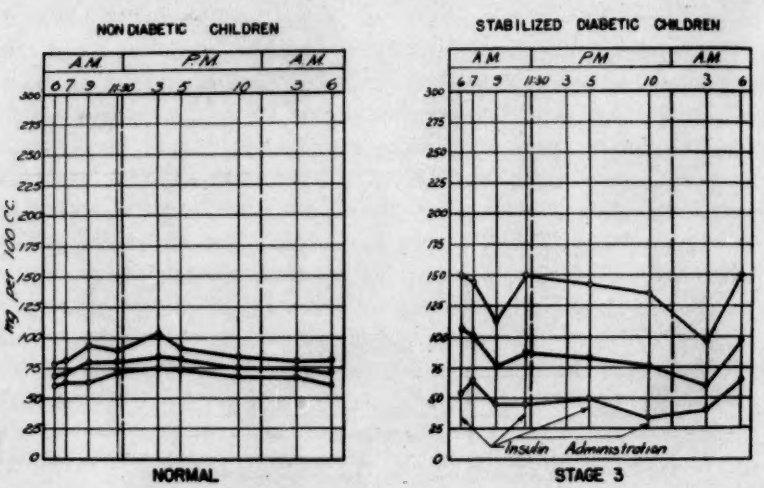


Chart 4.—The curves at the left represent diurnal fluctuations of the blood sugar level in 6 nondiabetic children receiving diets similar to those of the diabetic children but without administration of insulin. Nine determinations were made for each subject during two different twenty-four hour periods. The curves at the right represent diurnal fluctuations of the blood sugar level in 27 diabetic children after stabilization. The upper and lower curves represent single maximum and minimum values; the center curve represents the average of all diurnal determinations.

the hospital. Finger blood is wholly satisfactory for this purpose.[2] A fair interpretation of the diurnal fluctuations can be made from knowledge of the blood sugar level at three periods: first, prior to the morning dose of insulin; second, just before breakfast, after the dose of insulin has been active for a half-hour or longer; third, two hours after breakfast. When stability has been attained, the value should lie within the range shown in chart 4.

The distribution of insulin dosage requires further comment. The majority of our patients have needed four doses of regular insulin daily, distributed throughout the twenty-four hours as previously described, in order to maintain the desired level of stability. After stability has been reached, the midnight dose frequently can be given at 10 p. m. When the insulin requirement has not exceeded 1 unit for each kilogram of body weight, or a total of 20 units, it has been possible to reduce the number of injections to three or even two doses. Such patients have been maintained by means of one injection of protamine zinc insulin, with the same total unitage. The prolonged action of the slowly absorbed protamine zinc insulin tends to lead to insulin shocks of a type more difficult to recognize and to treat than those usual with overdosage of regular insulin.

Two types of insulin shocks were encountered in this study. The type commonly seen was ascribed to rapid lowering of the blood sugar level and was accompanied by signs of stimulation of the sympathetic nervous system. It usually was associated with a pathologically low blood sugar level, but not invariably so; one patient had definite signs of insulin shock with a blood sugar level of 188 mg. per hundred cubic centimeters. The second type of shock was more profound and serious; it resulted from excessive and continued overdosage of insulin with attendant exhaustion of the usual defense mechanisms against hypoglycemia. It was associated with blood sugar levels of 20 to 30 mg. The onset was insidious, and frequently the patient complained simply of headache, weakness or both. The patients passed rapidly into coma and frequently had convulsions. Overdosage of protamine zinc insulin usually caused this form of shock, and the period of recovery required several hours, in contrast to the early recovery when the more rapidly absorbable forms of insulin were used. The danger associated with the use of protamine zinc insulin should be kept in mind; it has led to needless fatalities.[3] With this form of insulin shock it was necessary not only to administer emergency treatment but also to keep the patient under careful observation for several hours to make sure that he did not lapse again into shock as a result of further absorption of insulin.

We recognize that numerous reports favorable to the slowly absorbed forms of insulin have appeared in the literature. So many studies with the new types of insulin have been made with the subjects in stages 1 and 2 of treatment that the conclusions drawn can be seriously questioned. This is especially apparent with reference to reduction of total insulin requirements. Using stabilized patients as subjects we have studied the relative efficiency of commercial supplies of regular insulin, protamine zinc insulin and zinc insulin crystals. These studies are

3. Jackson, R. L., and Boyd, J. D.: Dangers in the Use of Protamine Zinc Insulin, J. Iowa M. Soc. **38**:1, 1938.

still in progress. Up to the present time no clinically significant difference has been found between regular insulin and zinc insulin crystals.

Certain observers have commented on the so-called increase of dextrose tolerance which they have observed after various modifications of standard regimens of diabetic therapy. This has been characterized by the increased amounts of dextrose formers which the patient could utilize without glycosuria. Because our treatment includes a postulated constancy of diet, we have left the diet essentially unaltered during treatment and have measured improvement on the basis of decreased insulin requirement. While the terminology may be unimportant, we consider the improvement dependent on the restoration of the exhausted component of the sugar handling function through the supportive effect of treatment.

## ANALYSIS OF RESPONSE

Analysis of the average response of the 27 patients is shown in the table. The data are arranged according to the age of the patient

*Average Response of Twenty-Seven Diabetic Children to Regimen of Control*

| Age Group, Yr. | Number of Children | Duration of Disease, Mo. | Period of Observation | | | | Incidence of Mild Shock | | | | No. of Blood Sugar Determinations | Reduction of Insulin Need, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Stage 1 | Stage 2 | Stage 2B | Stage 3 | Stage 1 | Stage 2 | Stage 2B | Stage 3 | | |
| 2-11 | 10 | 1.6 | 7.8 | 18.5 | 4.6 | 28.7 | 0.3 | 3.0 | 0.0 | 0.4 | 142 | 68 |
| | 3 | 13.6 | 5.0 | 14.0 | 6.0 | 37.6 | 0.7 | 3.6 | 0.0 | 0.0 | 168 | 53 |
| | 2 | 35.5 | 9.0 | 19.5 | 25.0 | 23.5 | 0.0 | 6.0 | 10.0 | 6.0 | 209 | 52 |
| 11-16 | 4 | 2.7 | 14.0 | 20.0 | 4.2 | 17.2 | 0.0 | 0.5 | 0.0 | 0.0 | 107 | 46 |
| | 4 | 15.0 | 16.5 | 15.7 | 8.5 | 9.7 | 0.0 | 0.3 | 0.0 | 0.0 | 127 | 47 |
| | 4 | 100.0 | 11.0 | 11.5 | 8.7 | 2.0 | 1.5 | 3.0 | 1.5 | 0.0 | 80 | 32 |

and the duration of the disease, respectively. From these values one may draw the following inferences:

1. The younger patients and those having had the disease a shorter time showed greater reduction of insulin dosage during the period of metabolic recovery than did the older patients.

2. The younger patients showed evidences of shock during the period of metabolic recovery more frequently than did the older patients.

3. The older children required a longer period to attain aglycosuria prior to entering the period of metabolic recovery.

4. The patients who had been diabetic for a long time showed greater instability during management, as evidenced by greater frequency of shocks and a longer period of transition between the stage of metabolic recovery and that of true stabilization.

These generalizations are borne out also in the records of the other patients who are not included in this presentation. However, interpretation of their charts is made difficult because of complicating factors,

such as infection, alterations in diet prescription, variable physical activity, emotional disturbances, operative treatment or alterations in the dosage, type or distribution of insulin during the various stages of treatment.

## SUMMARY AND CONCLUSIONS

Using a constant regimen of treatment for a selected group of children with diabetes mellitus, we have continued detailed hospital control until stability of insulin requirement and normal range of fluctuations in blood sugar have been attained. The regimen employed has been based on the premise that physiologic levels of control (e. g., normal blood sugar levels, freedom from glycosuria or insulin shock and complete adequacy of diet) are desirable and attainable in the treatment of diabetes mellitus. On the basis of the data obtained the following conclusions are offered:

1. With strict hospital and laboratory control, a period of six weeks to two months is necessary to attain suitable stability of the sugar-handling function. Adequately prolonged hospital control of the patient at the outset of his management increases his subsequent stability under home management and avoids many of the difficulties which usually characterize the treatment of the diabetic child.

2. With the establishment of such stability the insulin requirement becomes much smaller than during periods characterized by mild glycosuria or hyperglycemia.

3. In view of this spontaneous lessening of the insulin requirement, many of the reported studies dealing with the relative value of different types of insulin are open to question as to conclusions drawn.

4. It seems probable that few children with diabetes mellitus in the country at large attain a desirable level of control, especially when preliminary stabilization is not complete and mild glycosuria so frequently is countenanced.

5. The plan of treatment described is practicable, and, whereas a strict regimen must be employed, this is stereotyped and can be placed within the facilities of physicians in most regions of this country.

6. With improvement of level of control, one may predict a lessening of complications, sequelae and fatalities from diabetes mellitus in children.

Drs. E. Van Epps and G. Wagner gave us cooperation in this study, and Drs. P. C. Jeans and Genevieve Stearns made suggestions concerning the preparation of the paper.

# DIPHTHERIA IMMUNITY AND FREQUENCY DISTRIBUTION CURVES FOR ANTITOXIN

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During the past several years a number of unrelated studies and investigations have amassed material which when put together forms an interesting picture of diphtheria immunity and factors affecting it in a community. Diphtheria antitoxin is at present the only readily measurable immune substance and its exact relation to a person's resistance to diphtheria is by no means fully comprehended. However, both the Schick test and the diphtheria antitoxin determinations on human serum provide methods for studying immunity to diphtheria in a population that should be instructive.

In anthropometric studies attempts have been made to correlate the susceptibility of persons with distinct body types to certain diseases. If variability in immunity to a given disease occurs and if that immunity is measurable, a frequency distribution curve for immunity in a cross section of the population comparable to the frequency curves for other characteristics should be possible. Variations in immunity were discussed in a paper in 1934,[1] and a probable distribution curve was drawn. Since that time, Dr. Mary Schmeckebier, fellow of the Fleischner Endowment Fund, has determined the diphtheria antitoxin content of blood serum according to a slightly modified Jensen [2] technic.

In the fall of 1938 when the routine Schick tests were made on the sophomore medical students, blood was taken for antitoxin determinations, and in the spring of 1939 when the immunized group was rechecked by repeated Schick tests, the determinations of antitoxin were also repeated. For comparison with the data for this adult group, Dr. Schmeckebier gave me her figures for the antitoxin content of 77 children immunized six months previously with two or three doses of toxoid, 0.5 and 1 cc. each, at three week intervals. No attempt will be made in this paper to differentiate or evaluate different methods of immunization. The children were immunized according to one of the many accepted methods and given Schick tests six months later. The adults were immunized as described later in this paper.

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From the Hospital for Children.

1. Thelander, H. E.: Individual Variations in Immunity, Am. J. Pub. Health **25**:737, 1935.

2. Jensen, C.: Die intrakutane Kaninchenmethode, Acta path. et microbiol. Scandinav., 1933, supp. 14, p. 1.

DIPHTHERIA ANTITOXIN FREQUENCY DISTRIBUTION CURVES

The determinations made it possible to plot the distribution of diphtheria antitoxin in two cross sections of the population. The results are recorded in charts. The cases are expressed in percentages of the total number so that all groups may be compared. These percentages are plotted against the amount of antitoxin units per cubic centimeter of serum and separated into five divisions in multiples of ten. Thus the amount of antitoxin ranged from 0 to 0.005 unit per cubic centimeter in the first division, 0.005 to 0.05 in the second, 0.05 to 0.50 in the third, 0.50 to 5 in the fourth and over 5 in the fifth. Antitoxin is not

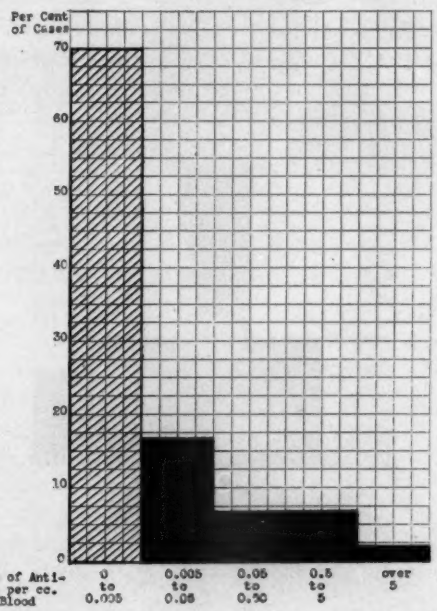


Chart 1.—Distribution of adults according to units of diphtheria antitoxin per cubic centimeter of blood prior to immunization.

accurately measured at 0.0005 unit, and very rarely will a person have more than 50 units, so that the extremes will not be out of proportion to the other divisions and the entire range of antitoxin values is covered.

Chart 1 shows the distribution of 50 students in the sophomore class in medical school in the fall of 1938 prior to the beginning of immunization. The shaded portion, which is in the 0 to 0.005 division, shows the per cent of those who usually have a positive reaction to the Schick test or are in the borderline group. It has been my experience and that of others in this field that the Schick test is usually negative if there is 0.005 unit of antitoxin per cubic centimeter of serum. With concen-

trations below this figure the test is usually positive, though at times it may be equivocal in this zone, and at times a negative reaction has been obtained with only 0.001 antitoxin unit per cubic centimeter. It will be noted that 70 per cent of the class had less than 0.005 unit per cubic centimeter of serum, but only 62.9 per cent had positive reactions to the Schick test. There was therefore a discrepancy of 7 per cent. From this high reading of 70 per cent in the low titer group there is a rapid drop to 16 per cent in the group with 0.005 to 0.05 unit of antitoxin, and beyond this is a gradual decline to less than 2 per cent with more than 5 units per cubic centimeter.

Chart 2 shows the distribution of the 29 students who had positive reactions to the original Schick test, five months after immunization. No one with a negative reaction was given the injections, even though

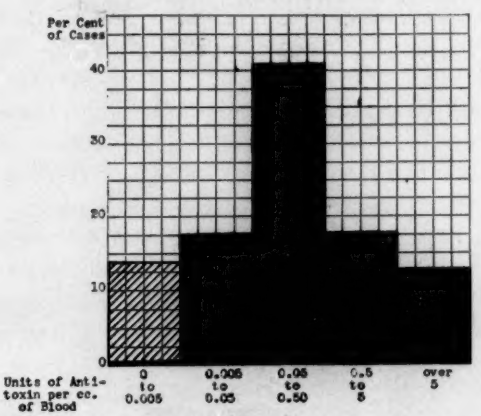


Chart 2.—Distribution of adults with positive reactions to the Schick test five months after immunization according to units of diphtheria antitoxin per cubic centimeter of blood.

the amount of antitoxin present was below the level of 0.005 unit per cubic centimeter. This group, therefore, represents the 62.9 per cent with positive reactions to Schick tests and not the 70 per cent with less than 0.005 antitoxin unit per cubic centimeter of serum. The distribution into a typical probability curve is interesting but not surprising. The chart represents the variations of persons with positive reactions to Schick tests in regard to their capacity to immunize. The majority fall into a middle group, with 0.05 to 0.50 unit of antitoxin per cubic centimeter, and then the numbers drop off rapidly both ways, with the serums of a few failing entirely to immunize and those of a few having the high titer of 5 units or above. It has been repeatedly emphasized that a small percentage of persons are very resistant to immunization.

Chart 3 is a combination of charts 1 and 2; that is, it represents the same 50 students after a period of five months and after those with positive reactions to the Schick test had been immunized. It includes those who were immune at the time of the preliminary test. The shift in the distribution is toward the low antitoxin side. The chart is given for comparison with the findings in the next chart.

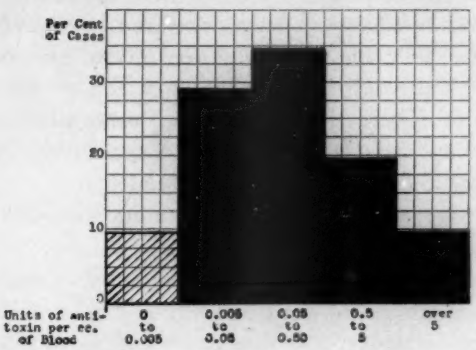


Chart 3.—Distribution of 50 immunized and naturally immune adults according to units of diphtheria antitoxin per cubic centimeter of blood.

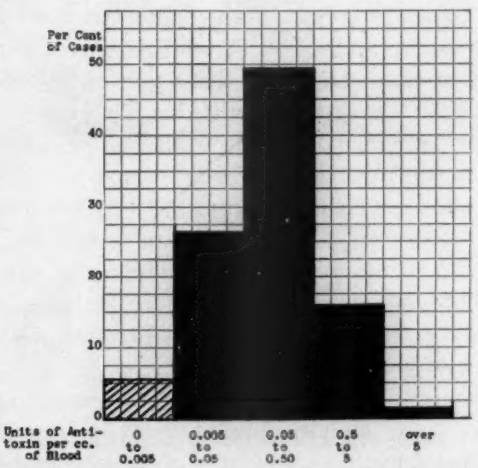


Chart 4.—Distribution of 77 immunized preschool children according to units of diphtheria antitoxin per cubic centimeter of blood.

Chart 4 represents a group of preschool children immunized with two or three doses of toxoid, 0.5 and 1 cc. each, at intervals of three weeks. The Schick tests and the antitoxin determinations were made six months after immunization. Although few of the subjects had 5 or more units the general distribution of the curve is the same as for the adult group.

There is a crowding into the middle divisions, with less tendency to fall into the divisions with either low or high immunity.

There are several pertinent differences in the groups of adults and of children: Children have less opportunity than adults to come in contact with diphtheria; few of these children had had previous Schick tests or injections of toxoid, and the children were not selected according to the results of preliminary Schick tests, as were the adults. In addition to this, it is possible and likely that children are more surely immunized than adults. If the older age group had been given the injections without a preliminary Schick test the distribution would probably have been somewhat different. There should have been more of a shift into the high antitoxin group, for 30 per cent of them already had between 0.005 and 5 units of antitoxin per cubic centimeter.

It is generally agreed that an initial stimulus with diphtheria toxin is essential to satisfactory immunization of a person. After a lapse of two or three weeks a second injection will then usually produce a prompt and marked rise in the antitoxin level. This rise is followed by a drop which is rapid at first and then more and more gradual, so that six months after the second injection the amount of antitoxin in the blood will have reached a practically stationary level somewhere above that which signifies immunity. If at any time another injection is given or if the person comes in contact with diphtheria, there should occur an immediate response. Among those who gave positive reactions to the Schick tests, 2 persons, each with 0.001 unit of antitoxin per cubic centimeter, continued to have little antitoxin; but in 3 others the antitoxin levels, usually between 0.0014 and 0.005 unit per cubic centimeter, rose to levels of between 0.1 and 2. One person had a false positive reaction with 1.6 units per cubic centimeter. He received the injections, and the second test showed 10 units per cubic centimeter. A student who had no reaction to the Schick test requested the injections on the basis that if a little immunity is good, more is better, and he was rewarded with a rise in antitoxin to over 40 units when tested five months after the injections.

Antitoxin determinations have been made by Jensen [3] and by Fraser and Halpern,[4] but these authors divided their subjects into different groups. Jensen shaded his like a spectrum, the lowest group being those with less than 0.0005 unit per cubic centimeter, the second group those with 0.0005 to 0.01 unit, the third with 0.01 to 0.1 unit and the last those with over 0.1. Fraser divided his subjects into groups with $\frac{1}{250}$ to

3. Jensen, C.: Active Immunization Against Diphtheria by the Combined Subcutaneous and Intranasal Method, Proc. Roy. Soc. Med. **30**:1117, 1937.

4. Fraser, D. T., and Halpern, K. C.: Diphtheria Toxoid, Canad. Pub. Health J. **26**:469, 1935; Serial Titrations of Diphtheria Antitoxin Following Toxoid, ibid. **26**:476, 1935.

1/100, 1/100 to 1/50, 1/50 to 1/10, 1/10 to 1/2, and 1/2 to 10 units per cubic centimeter. When Fraser's figures are plotted according to the groups in the distribution curve, the results from his group 1, with one dose of alum-precipitated toxoid after twelve to fourteen months, give a curve much like that on chart 1 of the students prior to immunization. The results from his group 2, with three doses of unmodified toxoid after twelve to fourteen months, assume much the curve of the group of children in chart 2 but with a greater shift to the left. The data for his final group, with the antitoxin present in the blood at the time of the injections of toxoid, show a curve very much to the right.

### IMMUNIZATION OF ADULTS WITH SMALL DOSES OF TOXOID

In 1934 [5] a report was made on the successful immunization of adults with small doses of toxoid. Through the cooperation of Dr. M.

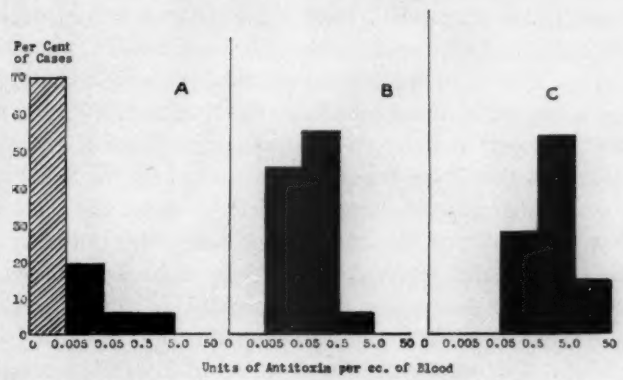


Chart 5.—Distribution curves of cases according to units of diphtheria antitoxin per cubic centimeter of blood (from figures by Fraser and Halpern [4]): *A*, antitoxin determinations twelve to fourteen months after one dose of alum precipitated toxoid; *B*, after three doses of unmodified toxoid, and *C*, after one dose of alum precipitated toxoid in persons with "natural" antitoxin.

S. Marshall, of the bacteriology department of the University of California, the study of the immunization of students has been continued. Each fall a group of 50 to 60 sophomore medical students and each spring an equal number of dental and pharmacy students have been given the Schick test, and those who gave positive reactions have been immunized. The material used for the Schick test has been ready-diluted Schick toxin and the corresponding control supplied by Cutter's Laboratory. In the preliminary tests done prior to immunization, the Schick toxin has been placed on the right forearm and the

5. Thelander, H. E.: The Immunization of Schick Positive Adults with Small Doses of Toxoid, M. Woman's J. **41**:255, 1934.

control substance in the corresponding position on the left arm. When the tests have been repeated after immunization the materials have been reversed, the Schick toxin being placed on the left and the control substance on the right arm. This has been done in order to obviate any possible interference of local immunity produced by the first injection of toxin. The reactions have been read one week after the test substances were applied, and in the great majority of cases have been so definite that a reading of positive or negative has been made without difficulty and usually without any valuable gradations of the reactions, such as 1, 2, 3 or 4 plus. In a few instances a descriptive remark has been added, such as "faintly positive," "positive but pale" or "hemorrhagic." Equivocal reactions were more common when the ready-diluted material first came into use. During the last four or five years there has been very little confusion in making positive readings. The control tests have rarely shown any reaction when read at an interval of a week. False positive reactions have been encountered in about 1 per cent of the adults. In these cases there has been no reaction about the control test but the site of the Schick test has been red or slightly hemorrhagic, like a bruise. Unless a Kellogg test (neutralization of standard toxin with antitoxin) is done or antitoxin determination are made, one cannot be certain that these reactions are not positive. However, after carefully analyzing several hundred Schick tests and controls, the examiner will suspect that the hemorrhagic reaction is not truly positive.

At the time of the reading of the test, those who had had positive reactions were given the first dose, 0.1 cc. of Cutter's toxoid (flocculation units 25 to 27 per cubic centimeters). The second and third doses were given at intervals of two weeks and were increased to 0.2 and 0.3 cc. respectively unless the first dose had given either a local or a general reaction. In case of untoward results with the first injection the subsequent doses were 0.1 cc. like the first one. Very occasionally even 0.1 cc. has given a severe enough reaction to necessitate discontinuing injections. The students have cooperated well and practically 100 per cent of them have had the Schick tests and have been given the injections.

The interval of two instead of three weeks has been used entirely for the students' convenience. It permits the tests and the three doses to be given in a semester without undue interference with holidays or examinations. The retests after immunization have been made during the spring semester, which makes the interval between immunization and rechecking a little short of six months. The pharmacy and dental students have been given the preliminary Schick tests and immunization during the spring semester, but it has been impractical to retest these groups six months later because of the scattering of the classes.

The 1934 report [5] on medical, dental, pharmacy and nursing students showed that 65.5 per cent gave a positive reaction to the Schick test. In the present series of 588 students studied between 1934 and 1939 the percentage of those with positive reactions was 53.9. This represents a drop of 11.6 per cent in the past five years and probably reflects an increasing number in this older group that have had previous immunization, Schick tests or some other contact with diphtheria toxin.

Immunization to diphtheria was introduced in San Francisco in 1920. By 1924 its routine use was adopted in the well baby centers and in the public schools of the city. Most of the present college students, therefore, even though they do not all come from this community, should give histories of childhood immunization. The students have been asked about previous immunization, and, although the histories cannot be entirely relied on, it is noteworthy that in 1937 34 per cent of the class gave a history of a previous Schick test, injections of toxin-antitoxin, injections of toxoid or diphtheria. In 1938 40 per cent of the class gave such histories. The drop in the percentage of those with positive reactions, therefore, is logical and should continue.

In 1934 89.1 per cent were successfully immunized, judging by repeated Schick tests; in the present report, for the period of the last five years, 91.6 per cent gave no reactions to the Schick test after immunization.

## IMMUNITY OF CHILDREN

In 1936 the County Medical Society of San Francisco, through a subcommittee on immunization, made a survey of the local community in order to determine the extent to which immunization to diphtheria was being carried out. Any testing of children based on volunteers would not be representative, since people who objected to immunization would probably also withhold their children from being given the Schick test. Another approach was therefore tried. The number of infants under a year old registered in well baby centers, in hospital well baby clinics and in pediatricians' well baby services was obtained. The number thus gathered represented 87.3 per cent of the population under 1 year of age in the city. In addition to this there was another group, not calculated, under the care of obstetricians and general practitioners. After due allowance was made for possible duplication of figures, it was estimated that over 90 per cent of the babies under 1 year of age were under medical supervision. All the agencies consulted reported that between 95 and 100 per cent of the babies were immunized.

As a check on these figures, Dr. Kathleen Kilgariff took careful histories on 100 children between 1 and 6 years of age who were on relief and attended the Central Medical Bureau. She found that 80 per cent of this group had been immunized.

Records from the Department of Health on the results of immunization in day nurseries, in public and parochial schools and in child welfare centers showed that about 80 per cent of the preschool and 60 per cent of the elementary school children were being immunized.

When these results are combined with figures obtained on testing the students at the Medical Center, the immunity of the population is approximately 80 per cent among children under 5 years of age, 60 per

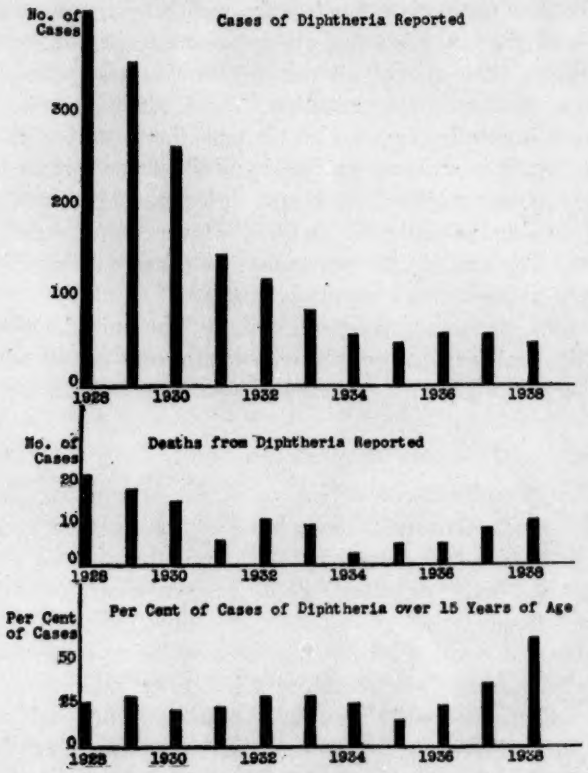


Chart 6.—Statistics on diphtheria in San Francisco from 1928 to 1938.

cent among children of elementary school age and 40 per cent among young adults.

A comparison of these figures with Zingher's [6] for New York in 1923 reveals almost a complete reversal of findings. Selecting from his figures those in comparable age groups, the immunity he found was

6. Zingher, A.: The Schick Test Performed on More Than 150,000 Children in Public and Parochial Schools in New York (Manhattan and the Bronx), Am. J. Dis. Child. **25**:392 (May) 1923.

17 per cent among children under 3 years of age, 68 per cent among children 9 to 10 years of age and 88 per cent among adults 20 to 30 years of age.

### DIPHTHERIA MORBIDITY AND MORTALITY

The shift of susceptibility to diphtheria from the young age groups to the adult group is not only interesting but pertinent. Chart 6 gives the incidence of diphtheria, the number of deaths and the percentage of cases in which the age was over 15 from 1928 through 1938 in San Francisco. There was a drop in the total number of cases from 415 with 20 deaths in 1928 to 43 with 1 death in 1934. Since 1934, however, the death rate has mounted, though the case reports have varied little. Analysis of the statistics shows that not only have the case reports shown an older age group with diphtheria, but the mortality rate among young adults has gone up. This shift was so significant that Dr. J. C. Geiger, director of public health of San Francisco, sent a letter to the physicians of his own department and a similar statement to the County Medical Bulletin for publication, warning the doctors to be on the alert for diphtheria in adults. This warning was timely, because physicians who think of diphtheria as a childhood disease may miss the diagnosis in the adult. It is, furthermore, becoming increasingly difficult to teach medical students to recognize the disease in either children or adults when the case reports in the community drop to insignificant numbers.

In this community, therefore, the decrease in cases of diphtheria and the shift of the reported cases from the young to the older age groups are consistent with the history of immunization and the finding, by the Schick test and by antitoxin determination, of a shift of those susceptible to diphtheria from younger to older people.

### COMMENT

A graphic representation of the distribution of diphtheria antitoxin in a cross section of the population gives a simple method for comparing different kinds and methods of immunization. During the days when toxin-antitoxin mixture was the agent used, it was revealed by Schick tests alone that the immunizing material was not satisfactory. Fraser's figures for the one dose of alum-precipitated toxoid when plotted according to the probability curve reveal very graphically the unsatisfactory results of this method. There is still a difference of opinion and practice in the choice of material, the interval between injections, the size of the dose and the number of injections. A study of the distribution according to the frequency curve should help clarify the questions involved.

The immunization of adults with small doses of toxoid for a period of ten years has given satisfactory results. It is unnecessary to subject

older children or adults to the risk of the severe reactions often accompanying injections of 1 cubic centimeter, nor is it necessary to resort to the use of the much less satisfactory toxin-antitoxin mixture.

The neutralization of toxin by antitoxin in geometric proportions is an interesting although not new finding.

The variability of herd immunity is brought out in these studies. Immunity is not static. It changes from one generation to another and is influenced by both natural and artificial factors.

384 Post Street.

# Case Reports

## HYPERTENSION IN EARLY CHILDHOOD

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The first record of hypertension in children was that of von Basch,[1] who worked in Morton's clinic in Vienna, Austria, about 1894. In 1903 Cook[2] took readings of blood pressure of sick children at the Johns Hopkins Hospital.

Of the numerous methods of determining blood pressure, the most practical and accurate clinically is still Korotkopf's[3] auscultatory method, which, by the use of a 9 cm. cuff, is a modification of the Riva-Rocci method. Certain authorities, such as von Recklinghausen,[4] claimed errors were frequently caused by the use of a too narrow cuff. That author insisted that one less than 10 cm. wide should never be used. Yet readings average only 5 mm. lower with the wider than with the narrower cuff, and the narrower cuff is more easily adjusted to the arm of a child.

The literature is replete with cases of great divergence in results. The diversities are dependent not only on the variations in the sphygmomanometer and in the method used but on the personal equation of both the experimenter and the patient. There are no absolute standards. The reason for this variance lies in the presence of certain physiologic factors, such as age, weight, sex, height, pulse rate, heredity, emotions and relation to meals, to sleep and to exercise. The blood pressure is higher with the patient lying than sitting and higher with him sitting than standing.

Age is the basis on which the standard of blood pressure has always been estimated. Katzenberger[5] developed a formula—80 plus 2x

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Read before the Pediatric Section of the Westchester County Medical Society and before the New Rochelle Hospital staff meeting.

1. von Basch, S. S. K.: Ueber Pulse Fühlen, Pulse Schreiben, und Pulse Messen, Arch. f. Kinderh. **7**:64, 1894; Ueber die Messung des Blutdrucks am Menschen, Ztschr. f. klin. Med. **2**:79, 1880.

2. Cook, H. W.: Clinical Value of Blood Pressure Determinations as a Guide to Stimulation in Sick Children, Am. J. M. Sc. **125**:433, 1903.

3. Korotkopf, M.: Blutdruckmessung im Kinder, Tr. Imp. Acad. Med., St. Petersburg **15**:365, 1905.

4. von Recklinghausen, H.: Ueber Blutdruckmessung beim Menschen, Arch. f. exper. Path. u. Pharmakol. **46**:78, 1901.

5. Katzenberger, A.: Puls und Blutdruck bei gesunden Kindern, Ztschr. f. Kinderh. **9**:167, 1913.

(x equaling the age in years). This was shown by Meyer,[6] however, not to apply to every age.

In infants blood pressure is affected by type of delivery, period of gestation, method of feeding and the other physiologic factors aforementioned.[6a] Higher readings may be due to illness associated with fever.

In normal children blood pressure is generally lower than in adults, increasing with age until at puberty it approaches that of the adult. The increase occurs approximately two years earlier in girls than in boys (at 9 to 11 years). This is possibly explained on an endocrine basis. As yet no definite differentiation between pathologic and physiologic hypertension has been brought forth; hence one must issue a guarded prognosis for preadolescent patients.

One of the most interesting phenomena of blood pressure is the sudden increase which appears at the beginning of adolescence and is followed by a postadolescent drop. William Fishbein noted a pressure of 140 and 160 mm. in well developed and well muscled boys between the ages of 14 and 16 years. Another group of adolescent boys in the same chronologic range who presented themselves because of epistaxis and pounding through the head after exercise had similar blood pressure, which dropped without any treatment shortly after they completed their adolescence.

The adolescent rise has been attributed to the change in ratio between the size of the heart and the size of the blood vessels, but this change does not explain the preadolescent rise or the postadolescent drop in blood pressure. These are probably due to the rearrangement of the internal secretions.

Factors other than age account for marked variation in the various age groups, chief among them being weight, height and circumference of the arm.

A progressive rise in systolic pressure affects also the diastolic. Adolescence seems to retard rather than accelerate diastolic pressure. The diastolic and the pulse pressure show a period of standstill which lasts until about the twelfth year, when they are again accelerated. Diastolic pressure, in contrast to systolic pressure, stays at an almost uniform level. The pulse pressure increases progressively and proportionately more than the systolic over the corresponding period.

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6. Meyer, E.: Blutdruckuntersuchungen an gesunden und kranken Kindern, Ztschr. f. Kinderh. **47**:560, 1929.

6a. Reis, R. A., and Chaloupka, A. J.: Blood Pressure in the Newborn Following Normal and Pathological Labor, Surg., Gynec. & Obst. **37**:206 (Aug.) 1923. Rucker, M. P., and Connell, J. W.: Blood Pressure in the Newborn, Am. J. Dis. Child. **27**:6 (Jan.) 1924.

REPORT OF A CASE

B. C., a white American girl aged 13 years, had had frontal headaches for two years, associated with nausea, vomiting and drowsiness. Approximately a year and a half after their onset they had become more frequent and severe, so that she had been unable to ascend stairs without becoming dizzy.

On admission to the hospital she had a pulse rate of 120, the beat being irregular and feeble. Her general nutrition and development were within normal limits. Her mind was clear, and she was cooperative but apprehensive. Her cervical lymph glands were moderately enlarged. The peripheral arteries were definitely sclerotic, and her blood pressure over the right arm was 190 systolic and 160 diastolic; over the left arm, 200 systolic and 76 diastolic; over the left leg, 150 systolic and 110 diastolic, and over the right leg, 210 systolic and 180 diastolic. There was moderate bilateral horizontal nystagmus. In the fundi were many patches of atrophic retinal choroiditis. Sclerotic arteries and small retinal hemorrhages were visible. The vision was diminished bilaterally so that it was difficult for her to count fingers. A correction of 20/200 was necessary for both eyes.

Throughout her sixty-four day stay in the hospital the systolic blood pressure ranged from 211 to 260, averaging 230, while the diastolic varied from 160 to 190 and averaged 164. The average pulse rate was 70. The systolic pressure was highest in the evening, fluctuating 10 to 30 mm. of mercury, and in the last seven days prior to her death it gradually decreased to 211 mm. Her diastolic pressure fluctuated.

There was no evidence of brain tumor. Her deep reflexes were equal but diminished. The neurologist's opinion was that the child was suffering from hypertensive encephalopathy.

The electrocardiogram showed no sign of any myocardial involvement except that in lead IV there was an abnormal QRS group.

The urine contained albumin graded 1 to 3; the specific gravity varied from 1.010 to 1.024, and there were many coarse granular and a few hyaline and fine granular casts. Urine taken in 1934, while the patient was at the clinic, had a specific gravity of 1.024 and was otherwise normal. In 1936, prior to an operation for removal of tonsils and adenoids, a specimen of urine had a specific gravity of 1.008 and was otherwise normal. A blood count at this time showed 4,800,000 red blood corpuscles and 92 per cent (14.3 Gm. per hundred cubic centimeters) hemoglobin. The differential count was normal. Red blood cells were occasionally seen in the urine varying from 25 to 30 to the high power field. The blood urea level varied from 27 to 46.5 mg. The creatinine and uric acid were within normal confines, but there was a slight increase—to 41.7 mg.—in the nonprotein nitrogen content. The total protein in the serum was 4.9 mg., of which albumin was 3.6 and globulin 1.3 mg. The McClure-Aldrich test showed disappearance of the reaction in forty-five minutes. There was an interesting increase in the cholesterol level, which varied from 400 to 712 mg. per hundred cubic centimeters. The remainder of the chemical composition of the blood was normal. The phenolsulphonphthalein test showed an excretion of 45 per cent in the first half hour, 10 per cent in the next half hour and 12 per cent in the second hour, making a total of 67 per cent. A repetition of the test about ten days later showed a decrease to a total excretory percentage of 50 (30 per cent in the first hour and 20 per cent in the second). The spinal fluid was under marked pressure, about 350 mm. The Wassermann reaction of the spinal fluid was negative, and the colloidal gold curve 1112100000. The hemoglobin concentration was 98 per cent; the red blood cell count 4,980,000, and the white

blood cell count, 13,800, with 65 per cent polymorphonuclears, 1 per cent eosinophils, 32 per cent lymphocytes and 2 per cent large mononuclear cells.

Roentgenograms of the long bones, kidneys and sella turcica were normal except for a slight clouding of the right ethmoid bone.

There was a daily variation of her fluid intake from 75 to 1,230 cc., while her output of urine varied from 0 to 1,250 cc.

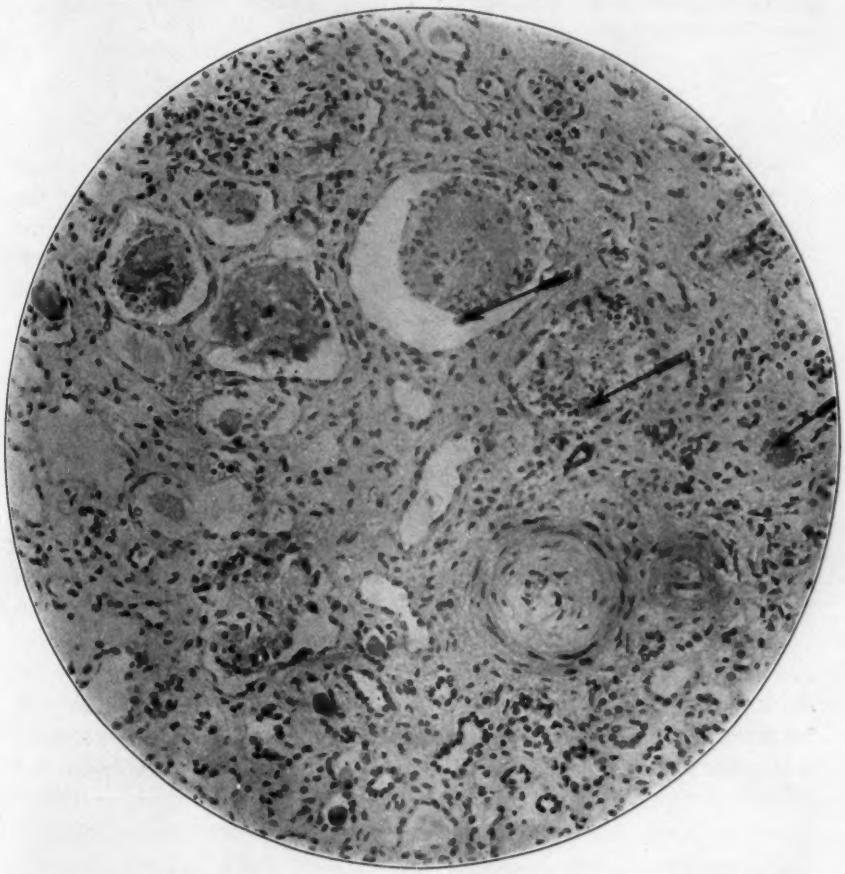
The Wassermann reaction of the blood was 3 plus with cholesterolized antigen and doubtful with acetone-insoluble antigen, but examination one week later gave negative results with both antigens.

The basal metabolic rate was + 8.1 per cent.

*Autopsy Data.*—At autopsy about 600 cc. of clear yellow fluid was seen in the abdominal cavity, and the coils of the small intestine were deeply cyanotic. The soft tissues of the mesentery contained excess fluid. The spleen was large, weighing 150 Gm. The liver was slightly enlarged, weighing 120 Gm., but was otherwise of normal structure. The most interesting observation at autopsy was that the left kidney was edematous and weighed 250 Gm. The capsule readily separated. The subcapsular surface was a pale pinkish gray, with many fine red dots (hemorrhages) just below the surface. The cut surface was pale pinkish gray. The glomeruli were not grossly visible; the tubules appeared as wide gray opaque lines. The renal vessels were thickened and contained yellow deposits of cholesterol. The right kidney weighed only 25 Gm. and was flat and bean shaped. Its ureter was small but traceable down to the bladder. The capsule separated readily, and the kidney externally and on section was pinkish gray. The pelvis was small but of normal shape. The bladder was small and contracted. Both pleural cavities contained a small amount of clear fluid—about 50 cc. There were some thick fibrinous adhesions about the lower lateral margin of the left lobe. The pericardium was enlarged and its walls thickened and edematous. Section showed it to contain about 50 cc. of slightly cloudy fluid. In the upper part of the sac there were fibrinous adhesions between the pericardium and the epicardium. These formed a thick layer over the surfaces of the auricles and posterior surface of the right ventricle. The heart was enlarged, weighing 300 Gm. The left ventricle was hypertrophic. On section the aortic and mitral cusps were seen to be thickened and white, but there were no vegetations on their surfaces. There were yellow deposits of cholesterol in the substance of the valves and in their bases. The aortic cusps of the mitral valve contained the most yellow pigment. The endocardium was smooth throughout all the chambers of the heart. The coronary arteries were much thickened. There were numerous cholesterol plaques in their intimal surfaces. The cardiac muscle was pale red and showed decided loss of color. In the wall of the left ventricle there were numerous irregularly shaped white areas. These were mainly 2 or 3 mm. in diameter. The aorta was of normal size and shape, but its walls were apparently thicker than normal. Section showed yellow plaques of considerable size in the intima. The branches of the aorta were all thickened and contained plaques. The bones of the skull appeared normal. The dura was of normal color and thickness. The brain weighed 1,300 Gm. It appeared large for the size of the subject and was certainly unusually heavy. The pia-arachnoid was of normal thickness, and there was increased fluid in its meshes. The vessels of the base were thickened and contained large atheromatous plaques. Section showed the brain substance to contain excess fluid. The ventricles were of normal size and shape and contained a normal amount of fluid. The middle ears appeared normal on section.

The anatomic diagnoses were subacute diffuse nephritis, rudimentary right kidney, fibrinous pericarditis, cardiac hypertrophy, focal necroses in the cardiac muscle, early vascular atheromatosis and edema of the brain.

*Histologic Examination.*—Sections of the left kidney showed extremely complicated changes involving all elements. Most of the tubules in the cortical portion were dilated into small cysts and contained dense hyaline casts. Some



Section of the midcortex of the kidney, showing degenerating glomeruli, marked subintimal thickening of a small artery and recent thrombosis of a small contiguous artery.

of the larger tubules in the medullary portion contained casts, which were made up largely of leukocytes and cellular debris. The glomeruli were in part normal, and about half of them showed marked thickening of the tufts and adhesions to the capsules, and coarse hyaline thrombi were within the tufts. These thrombi contained no definite fibrinous network and only few cellular elements. The renal vessels, particularly the smaller arteries, showed marked thickening, with almost complete obliteration. Some of the larger vessels showed rather marked

thickening. Scattered through the cortical portions were large areas of hemorrhagic necrosis in which cellular outlines were just visible.

Sections of the right kidney, which was rudimentary, showed about the same changes as the left.

Sections of the liver showed marked granular degeneration of the hepatic cell. The margins were indistinct.

Sections of the brain showed marked intercellular edema.

The diagnoses were chronic diffuse nephritis, probably primarily vascular and recent hemorrhagic necrosis of the kidney.

### COMMENT

Probably this case is analogous to those described by Volhard as instances of the ischemic final stage of nephrosclerosis. In this case stress was laid on a renal lesion and its relation to the course of the disease, although its malignant character could be recognized at a time when impairment of renal function could not be discerned. Objections have been raised against this intimate relation between the condition of the kidney and malignant hypertension. The reports of Keith, Wagener, Kernohan and Anderson [7] and of Amberg [8] all led to the conclusion that a syndrome of malignant hypertension exists, characterized chiefly by persistent hypertension, absence of higher grades of anemia, adequate renal function at a time when striking lesions of the eyegrounds are visible and a rapid and fatal ending. The main histologic changes are situated in small arteries and arterioles, while the larger arteries and capillaries may be comparatively free from change. The most important and constant feature is the extreme diffuseness of the lesion. All the organs and tissues and even the vessels of the gastrointestinal tract and the skeletal muscles are severely involved, and sometimes the kidney, the heart or the brain to a greater degree than the others. In some arterioles the intima is hyperplastic; the muscular coat may be thickened or the lamina elastica hypertrophied and split. These changes can interfere with the blood supply to such an extent as to lead to secondary lesions in various organs. It must be remembered that children can die of hypertension without any renal manifestations, if one judges by the work of Keith and his associates with adults.

The presence of renal involvement at a given time cannot be regarded as sufficient cause for a diagnosis of so-called nephritic hypertension.

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7. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: Arterioles in Cases of Hypertension, ibid. **44**:395 (Sept.) 1929. Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, ibid. **34**:374 (Sept.) 1924.

8. Amberg, S.: Hypertension in the Young, Proc. Staff Meet., Mayo Clin. **3**:245 (Aug. 22) 1928; Am. J. Dis. Child. **37**:335 (Feb.) 1929.

As to the causes of hypertension, Kahler's[9] classification is best adhered to. It follows:

A. *Functional*
1. Central
   a. Primary
      (1) Psychic
      (2) Mechanical (intracranial)
      (3) Lesional (organic lesions in vasomotor area)
      (4) Toxic
   b. Secondary—reflexly (from vessels or from organs)
2. Peripheral
   a. Primary
      (1) Toxic
   b. Secondary—reflexly (peripheral from all vessels)

B. *Anatomic*
1. General or extensive organic constriction of the arterioles.

The malignant hypertension in the case here reported, according to this classification, would come under the second main heading, anatomic hypertension due to general or extensive organic constriction of the arterioles.

One cannot help but consider the condition as true malignant or essential hypertension when the entire history is reviewed. This conclusion is based on the following facts:

1. There was a normal fluctuation of the specific gravity of the urine, 1.008 to 1.024. The urine in 1934 and two years subsequently was essentially normal, with little chemical change.

2. The child had had pertussis, measles and an occasional sore throat. There were no symptoms in the preceding history indicative of acute glomerular nephritis or of chronic diffuse nephritis of the primary renal type, which often has a history of acute nephritis or sepsis with the blood pressure characteristically normal or, if elevated at all, rarely above 150 mm.

3. The blood counts and determinations of hemoglobin at no time showed evidences of hypochromic anemia, frequently seen in hypertension secondary to nephritis.

4. The absence of marked urinary albumin and any marked edema, together with the normal serum protein level without reversal of the albumin-globulin ratio and the normal McClure-Aldrich reaction,

9. Kahler, H.: Die Blutdrucksteigerung, ihre Entstehung und ihr Mechanismus, Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1924.

would tend strongly toward ruling out nephrosis in its true form or nephrosis with a nephritic syndrome.

5. The rapid and progressive course of events—covering approximately eighteen months—with the extremely rapid spurt in the last two months, associated with rapidly failing vision and absence of uremia, points strongly to malignant hypertension.

6. Finally, the postmortem data, especially the marked thickening, even to obliteration, of the arterioles, most marked in the renal and coronary arteries, indicate hypertension.

Amberg in 1929 described 3 cases of similar involvement, but unfortunately failed to report the results of postmortem examination.

## TREATMENT

Treatment is unsatisfactory.

Hot baths, administration of nitrites and phenobarbital and injection of foreign protein and liver extract are recommended. At times a nitrite and phenobarbital together produce a transitory fall in blood pressure. Neither a strictly salt-free diet nor treatment with potassium gives especially helpful results.

Blackfan and Hamilton[10] obtained good results by intravenous injection of magnesium sulfate in cases of acute glomerular nephritis with hypertension and cerebral edema. Phlebotomy may help.

Some patients' general condition improves without any fluctuation in blood pressure, and some feel better with a slight downward fluctuation of blood pressure.

Lumbar puncture does not produce any striking effect.

Rest with its restricted activity benefits most of the patients. Activity aggravates the condition. A diet containing 1 Gm. of protein per kilogram of body weight is sufficient.

Administration of chloral hydrate appears effective in cases of vomiting. Focal infection and existing complications should be treated. It is most important in treating hypertension to restrict activity, with periods of complete rest. It is also important to keep up morale, as the disease may last years. Most of the aforementioned treatment was tried in this case, but to no avail.

## SUMMARY

This case brings forth the old controversy: Is there ever an essential or malignant hypertension, or is hypertension secondary to chronic nephritis of the arteriosclerotic type?

10. Blackfan, K. D., and Hamilton, B.: Uremia in Acute Glomerular Nephritis: Cause and Treatment in Children, Boston M. & S. J. **193**:617 (Oct. 1) 1925.

Chronic nephritis may or may not be associated with hypertension. Increased arterial tension is always present in

*(a)* Chronic diffuse nephritis of the primary renal type with a history of acute glomerular nephritis or prolonged sepsis, or

*(b)* primary arteriosclerotic chronic diffuse nephritis with secondary contraction of the kidney. Chronic diffuse nephritis of the primary renal type without a history of acute nephritis or sepsis is characterized in most cases by a normal blood pressure, which is rarely above 150 mm.

It is dangerous to place diagnostic reliance on only one Wassermann test. False readings may be obtained because of extraneous conditions. In this case a cholesterol content of the blood of 712 mg. could easily have been the cause of a strongly positive Wassermann reaction.

400 Webster Avenue.

# PAROXYSMAL TACHYCARDIA

## REPORT OF TWO CASES

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AND
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Two cases of paroxysmal tachycardia demonstrated certain unusual features which appeared to warrant their being reported:

CASE 1.—*History.*—J. E., a girl aged 13, was admitted to the Hospital for Sick Children Aug. 25, 1938. She was the third child in a family of 6. The rest were in good health except for one who had mild kidney trouble and one who occasionally had bronchitis. The patient had usually been in good health. She had measles at the age of 4 years. At 7 she began to have tachycardia at intervals, the attacks lasting from a few minutes to four days. They were usually characterized by the sudden onset of a choking feeling which lasted a few minutes and was followed by a sense of weakness. At such times her heart rate was reported to be close to 200 beats per minute. Often her pulse was difficult to count because of the extremely fast rate. The onset of attacks was occasionally, but not usually, preceded by some excitement. One attack was initiated by her falling down stairs. Three came on while she was eating meals. One occurred during physical activity. None appeared to be initiated by infections. The intervals between paroxysms varied from a few days to several months. After each attack she felt weak and exhausted for two or three days, and often she had a mild headache.

There was no history of rheumatic fever or of chorea or of symptoms suggestive of these. Infections of the upper part of the respiratory tract were rare. Her appetite was excellent, and bowel movements were regular. Her menses began when she was 12 years old and had been regular since then, with a normal flow. She was menstruating at the time of admission to the hospital and said that she was more liable to attacks during menstrual periods. The present attack began while she was eating supper. She had a sudden choking sensation and then felt as if her heart had stopped beating. She had been well during the day and had had no premonition of the attack.

*Physical Examination.*—On admission to the Hospital for Sick Children, the child's temperature was 99 F., her pulse rate 200 and her respiratory rate 22. She was well developed, somewhat obese, very apprehensive and almost afraid to move. The pupils reacted to light, and slight strabismus was present. The ears were normal. The teeth were in excellent condition. The tonsils were not enlarged but were cryptic. The breasts were of the enlarged adolescent type. The lungs were resonant throughout, and no adventitious sounds were heard. Breathing was shallow. The heart beats were regular, with a rate of 200 to 210. The heart

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sounds were distinct but not loud. No murmurs could be heard. The blood pressure was 98 systolic and 78 diastolic. The abdomen was soft. The liver and spleen were not enlarged.

*Laboratory Examination.*—The urine was normal. The reaction to a tuberculin test with a dilution of 1:400 was negative. The basal metabolic rate was + 90 per cent. There were 4,700,000 red blood cells and 10,400 white blood cells, with 66 per cent polymorphonuclears and 34 per cent lymphocytes. The erythrocyte sedimentation rate was 2 mm. in one hour. The electrocardiograph showed tachycardia, with a rate of 200 to 210 beats per minute. The origin of the beat was not clear, but the pacemaker appeared to be in the sinus node. $P_1$ and $P_2$ were upright, but $P_3$ was inverted.

*Progress.*—The attack lasted for two weeks, and during the second week the patient gradually showed signs of heart failure.

On admission she was given a high caloric and soft diet. Phenobarbital was used as a sedative at first, but bromides were later substituted. Since other attacks had subsided within two or three days, it was anticipated that similar relief would occur from the present attacks. However, the tachycardia continued persistently, with a rate of 210 to 230 beats per minute, and it was decided to try the effect of mecholyl.

One of us has used mecholyl with normal children and found that in doses of 0.5 to 1 mg. it caused transient flushing and an increase in the heart rate followed by a decrease in the heart rate. These were smaller doses than those reported in the literature, but occasionally cardiac standstill was produced with relatively small doses. There was an accompanying drop in blood pressure in some cases.

In this case 0.5 mg. of mecholyl was injected subcutaneously, with no effect, on August 29. A few hours later 1 mg. of the drug was used, but no decrease in the heart rate was observed. The next day 1.5 mg. was given, but again no alteration in the rate was observed. In view of the drop in blood pressure sometimes observed with this drug, it was considered unwise to push the treatment any further.

Wright [1] recently reported a case of paroxysmal nodal tachycardia treated with mecholyl. Cardiac asystole was produced by 5 mg. of the drug. Later, however, much larger doses were given without untoward effect. In the case reported here all previous attacks had subsided within a day or two, and at the time mecholyl was used the most conservative methods of treatment seemed indicated.

On September 1, one week after the onset, the liver was palpably enlarged and the patient complained of pain in the epigastrium. Slight cyanosis was present. On September 3 the temperature became elevated to 101 F. The next day the respiratory rate became elevated to 30 to 40 per minute and signs of congestive heart failure appeared in the lungs. The liver was now palpable 3 fingerbreadths below the costal margin. The left border of the heart was enlarged well out into the axilla.

1. Wright, F. H.: Paroxysmal Nodal Tachycardia Treated with Mecholyl, Am. J. Dis. Child. **56**:1334 (Dec.) 1938.

On September 5 the patient was given 50 cc. and three days later 100 cc. of 25 per cent dextrose intravenously.

The administration of digitalis had been started on August 29 but was discontinued when it was decided to use quinidine sulfate. One grain (0.06 Gm.) of quinidine was given on September 6, but its administration was followed by vomiting. This dose was repeated the next day but again resulted in vomiting. On Septmeber 8 the patient was placed in an oxygen tent. The following morning the pulse rate had come down from 230 to 100 and she appeared much improved. During the afternoon the rate rose again to 200, but it shortly returned to normal and continued so.

Roentgenograms of the heart (taken at a distance of 7 feet [2.11 meters]) at various stages of her attack show interesting changes. One taken on September 10 showed gross enlargement of the heart, the apex appearing almost against the lateral wall of the chest. The lungs showed the cloudiness of congestive failure. The erythrocyte sedimentation rate after fourteen days of tachycardia was 8 mm. in one hour, the upper limit of normal with the method used (Landau, 1932). After the paroxysm ceased, the signs of congestive failure soon disappeared. The liver returned to normal size, the lungs became clear and the general appearance of the patient improved rapidly. The roentgenogram taken two and one-half weeks later, on September 28, showed a marked diminution in the size of the cardiac shadow.

The patient improved steadily after September 18, when the heart rate became normal. By September 28 her heart had returned to its normal size and she appeared well. It was decided to perform a tonsillectomy, but when the patient heard that she was to have her tonsils and adenoids removed, she became agitated. On October 1 her pulse rate suddenly went up to 200 again. This time she was put in an oxygen tent immediately, where she was quite comfortable, and the heart rate returned to normal three days later. On October 4, a few hours after normal rhythm had been established, a roentgenogram of the heart was taken, which showed that the cardiac shadow had increased notably in size. A pulmonary systolic murmur and a faint mitral systolic murmur were present at this time. On October 5 the pulse rate was elevated to 200 again for a few hours and then returned to normal, where it remained during the rest of the child's stay in the hospital. Successive roentgenograms showed that it took one week for the heart to return to normal size. After two weeks in bed she was allowed to get up gradually. The administration of quinidine sulfate was begun in small doses, and the amount was gradually increased to 130 mg. three times a day with no ill effects. On October 27 she was discharged.

The roentgenograms shown in figure 1 represent different phases of her recent illness. *C* was taken at the end of the attack which lasted two weeks, *B* after three days of tachycardia in her second attack and *A* after her heart had returned to normal. They all fit together, however, to indicate the degree of dilatation that had taken place in a short period.

*Summary.*—A 13 year old girl was admitted to the hospital suffering from paroxysmal tachycardia. The heart continued at a rate of more than 200 for fourteen days before returning to its normal rate and rhythm. During the second week of the attack she showed progressive signs of heart failure. Various drugs, such as sedatives, mecholyl, digitalis and quinidine, were given without beneficial effect. She seemed to improve somewhat in an oxygen tent, and this may have been instrumental in aiding the return of the heart rate to normal. The roentgenograms taken at the end of the attack show gross cardiac enlargement.

A second attack, which came on three weeks later and appeared to be initiated by anxiety, lasted three days, during which time the child was kept in an oxygen

tent. Roentgenograms taken before and immediately after this attack show a striking difference in the size of the cardiac shadow, the shadow in the one taken after the attack being noticeably larger.

The most interesting feature about this case was the rapid enlargement of the cardiac shadow as shown by a roentgenogram taken at 7 feet (2.11 meters). In the second attack marked enlargement took place over a three day period. From the appearance of the cardiac shadow, this

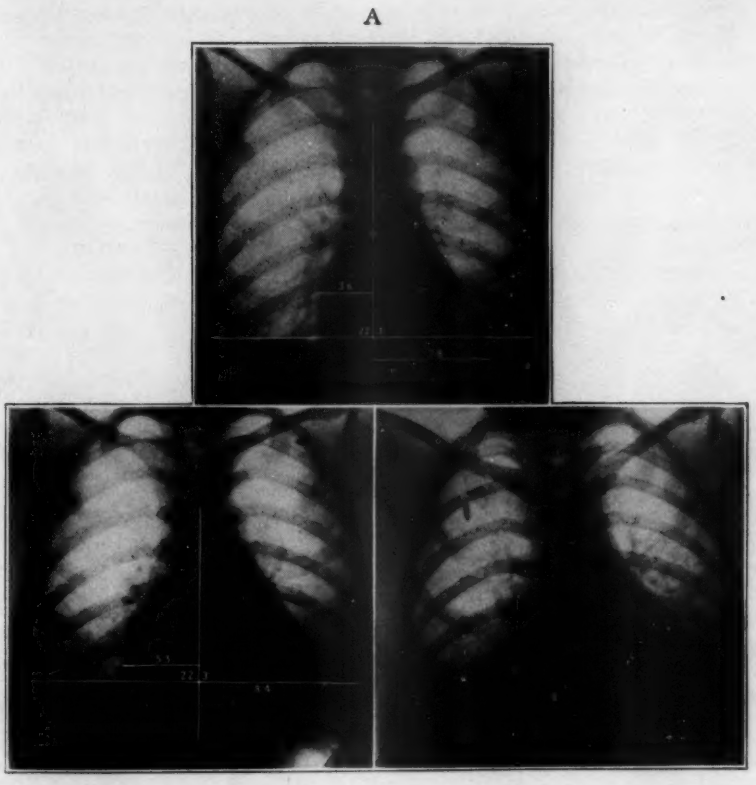


Fig. 1 (case 1).—Roentgenograms taken from a distance of 7 feet (2.11 meters): *A*, after the heart had returned to normal size; *B*, after three days of tachycardia with a rate of 210, and *C*, after two weeks of tachycardia with a rate of 210 to 230.

would seem to have been in all the cavities of the heart but particularly in the auricles. The change in cardiac size was associated with a loud pulmonary systolic murmur and a faint mitral systolic murmur. These signs were of course not appreciable until the heart rate had returned to normal, but even then they were not as great as one might have expected to accompany the degree of cardiac enlargement. Since the

increase in size of the heart appeared and receded in the course of one week, it was undoubtedly due to dilatation. The rapidity of the alterations would appear to justify the application of the term acute dilatation.

CASE 2.—*History.*—H. D., a Jewish boy aged 13, was the fourth child in a family of 4. The others were in good health. There was no history of rheumatic fever or heart disease in the family. The patient's health had been essentially good. He had measles in 1928. At the age of 6½ years, the school physician noticed that he had a fast and irregular heart action. He was well otherwise and had no symptoms of rheumatic fever or other disease. He was admitted to the Hospital for Sick Children in November 1931 for investigation of the reported cardiac irregularity. During his five days' stay in the hospital no abnormality in rate or rhythm was found. No cardiac murmurs were present. His electrocardiogram indicated a sinus rhythm with a rate of 87 and a PR interval of 0.16 second. The upstrokes of $R_1$ and $R_2$ were slightly slurred. $QRS_3$ was notched. There was beginning left axis deviation. His tonsils and adenoids were removed at that time.

Thereafter he was seen frequently in the outpatient department. His heart rate was usually rapid, at each visit being around 130. Frequently a sudden pause was heard in the fast rate, and two beats at a more normal rate were interjected. He had an occasional cold or sore throat, but his general health was excellent. He played some of the games of the boys in the neighborhood but was not quite as active as the rest. He did not tire easily or get out of breath. His appetite was good.

*Physical Examination.*—The patient was fairly well developed but a little underweight. The teeth were in good condition. The tonsils and adenoids had been removed. The lungs were normal. The heart was not enlarged, the heart sounds were of good quality and no murmurs were present. The heart rate at the last examination was 150. At varying intervals, usually every fifteen beats, a sudden pause in the fast rate occurred and two normal beats were interjected. Then the fast rate would be resumed. These pauses of two normal heart beats could occasionally be initiated by having the patient hold his breath, but after 2 such beats the rate and rhythm returned to their abnormal way in spite of continued holding of the breath. The electrocardiogram showed many interesting findings (fig. 2). Auricular tachycardia in which the heart rhythm was set by an ectopic focus in the auricle was indicated by the inverted P waves. The rate was approximately 150 beats per minute. The down stroke of the R wave was slurred in leads II and III. $T_3$ was inverted. At varying intervals the heart would resume a more normal rate and rhythm. These episodes would last for two beats only and were usually followed by one or two extrasystoles. The P wave became upright and the slurring of the R wave diminished in lead III. The T wave also became upright.

Recently the boy spent the night in the hospital, and his pulse rate during sleep was taken at intervals. It was found to be between 80 and 90 and often noticed to be irregular. When he was awakened or disturbed the rate became elevated again to about 116 and then gradually returned to a level of between 80 and 90. Examination of his heart or any slight disturbance increased the rate markedly. There was still an irregularity of the heart beat at the slower rates. The heart apparently contracted at a normal rate for a long interval and then a short run of faster beats appeared. Extrasystoles also occurred (fig. 2).

The roentgenograms of the heart, taken at 7 feet and at various angles, showed no enlargement or abnormality in any of the chambers of the heart. The diagnosis was paroxysmal auricular tachycardia due to an ectopic focus in the auricle.

*Summary.*—A 13 year old Jewish boy seen in the outpatient department had tachycardia and cardiac irregularity. Apparently a similar finding was noticed by the school physician seven years before, but no abnormality of the heart was found at that time on further investigation.

In recent studies the tachycardia has been shown to be of auricular origin and coming from an ectopic focus. The pauses were due to a temporary return to normal rhythm. The tachycardia (rate, 130 to 150) was noticed on several visits to the outpatient department in the past five or six years, but the patient continued in good health with little or no limitation in normal activity. Roentgenograms showed no increase in size in any of the chambers of the heart.

It appears probable that the patient was having frequent attacks of paroxysmal auricular tachycardia (rate, 130 to 150), which might in some instances have been due to excitement, since they disappeared at home and when he was in the hospital for several days. These

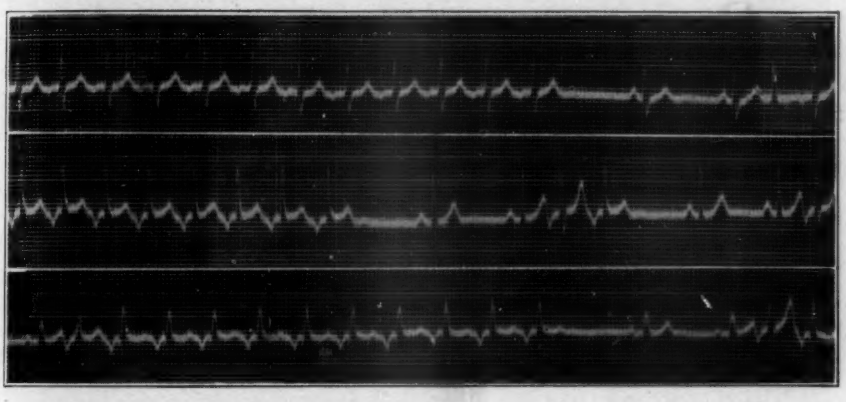

Fig. 2 (case 2).—Electrocardiogram taken Jan. 16, 1939, showing abnormal rhythm.

attacks were not associated with any demonstrable cardiac lesion, there was no history suggestive of heart disease and the general health was good. Most children with paroxysmal tachycardia whose cases have been reported have shown evidence of heart disease or have had a history suggestive of myocardial involvement. In 1936 Weiss and McGuire [2] described 2 patients with paroxysmal auricular tachycardia who had had tachycardia almost continuously for many years and in most respects were similar to this child. Another point of interest is the fact that this child's heart did not show any alteration in the sounds or the presence of any murmurs or enlargement, in spite of the repeated finding of the fast rate. At this level of tachycardia (rate, 130 to 150) there is apparently no adverse effect on the myocardium from the fast rate alone.

2. Weiss, H. B., and McGuire, J.: Am. Heart J. **12**:585, 1936.

COMMENT

These 2 cases of paroxysmal tachycardia are of interest for several reasons. This condition is rare in children, and only a few reports are to be found in the literature.

In 1937 Taran and Jennings [3] reported an interesting case of nodal paroxysmal tachycardia and, at the same time, summarized the literature to date. They found that 52 cases of paroxysmal tachycardia in children under 15 years of age had been reported from 1892 to 1935. The disease is probably not as rare as this number indicates, and many cases must have occurred which have not been reported, particularly of the milder variety. In those reviewed by Taran and Jennings the condition was ascribed to a variety of causes, the chief ones being congenital heart defect, rheumatic fever, whooping cough, syphilis, tonsillitis and extracardiac disturbances of the nervous mechanism. In contradistinction to adults, many of the children had evidence of underlying myocarditis and few had attacks not associated with some infection. The signs and symptoms showed considerable variety, but cardiac dilatation with dyspnea and cyanosis were reported most frequently. The prognosis appeared to depend on the underlying cause rather than on the type of arrythmia.

One of the 2 children reported on here was apparently so little affected by the attacks that he was hardly conscious of them and they did not interfere with his usual activities. In the other patient no definite evidence of active myocarditis could be found, and she was perfectly well between attacks. A striking finding in the latter child was the rapid and marked enlargement of the heart during the paroxysm It is also of interest that the other child showed no evidence of cardiac enlargement in spite of frequent paroxysms.

Not much attention has been paid to the change in the size of the cardiac shadow as shown by roentgenograms in cases of paroxysmal tachycardia, although such change has been thought to occur in varying degrees in many cases.

In 1932 Shookhoff and his associates [4] reported 4 cases, in 2 of which there was marked enlargement of the heart. In the other 2 slight dilatation was recorded. They suggested that a combination of factors of neurogenic and cardiac origin may produce the paroxysms in many instances.

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3. Taran, L. M., and Jennings, K. G.: Paroxysmal Atrioventricular Nodal Tachycardia in the Newborn Infant, Am. J. Dis. Child. **54**:557 (Sept.) 1937.

4. Shookhoff, C.; Litvak, A. M., and Matusoff, I.: Paroxysmal Tachycardia in Children: Report of Four Cases and One Postmortem Examination, Am. J. Dis. Child. **43**:93 (Jan.) 1932.

MacKenzie [5] in 1908 referred to the rapid cardiac enlargement of paroxysmal tachycardia, which, he said, may take place in a few hours and sometimes leads to edema and other signs of failure in twenty-four hours. His observations were of course without the help of roentgenology.

In 1915 Lewis [6] emphasized a divergent point of view. He said that there is a decrease in the size of the heart when it begins to beat more rapidly, but he pointed out that in long-continued paroxysms, especially when the reserve power of the ventricle is imperfect, the heart dilates.

Levine and Golden [7] in 1922 made roentgenologic studies on 11 patients with paroxysmal tachycardia and found no appreciable dilatation in 8. In 2 there was slight but definite enlargement, and in 1 the enlargement was considerable. They used the transverse diameters of the heart to compare changes, and roentgenograms were taken of 4 of the patients at 30 inches instead of 7 feet. The patient in whom considerable dilatation could be demonstrated had a much faster heart rate (250) than the others. Most of the patients had heart rates averaging 150 to 160. Two, however, had rates of 220 and 233, respectively, the attack of the first lasting for four and a half days and that of the second for two hours. Neither of these showed any appreciable dilatation as measured by the transverse diameter in the roentgenograms.

More recently, Parkinson [8] reviewed this question and referred to a patient he had under observation whose attack lasted twenty-one days and caused some enlargement though not much. He was unable to confirm the idea that enlargement takes place quickly after an attack begins.

Recently [9] a case of paroxysmal flutter with a 1 to 1 conduction and an auricular rate of 280 was observed roentgenologically. Two hours after the onset of the paroxysm enlargement of the heart and venous stasis were found.

Of the 2 patients whose cases are reviewed here, the first showed marked enlargement of the cardiac surface in three days. This was considerably greater than could be accounted for by phase of respirations or systole. After two weeks of continuous tachycardia, the cardiac shadow indicated that gross enlargement had taken place. One week

5. MacKenzie, J.: Diseases of the Heart, London, H. Frowde, 1908, p. 199.

6. Lewis, T., in Osler, W., and McCrae, T.: Modern Medicine, ed. 2, Philadelphia, Lea & Febiger, 1915, p. 87.

7. Levine, S. A., and Golden, R.: Paroxysmal Rapid Heart Action with Special Reference to Roentgen-Ray Measurements of the Heart in and out of Attacks, Arch. Int. Med. **29**:836 (June) 1922.

8. Parkinson, J.: Lancet **1**:1337, 1936.

9. Kahlstorf, A.: Klin. Wchnschr. **15**:1028, 1936; abstracted, Am. Heart J. **14**:508, 1937.

after the attack ceased the heart was much reduced in size, and it had apparently returned to normal at the end of three weeks. The rapidity of these changes indicated that the enlargement must have been due to dilatation of the cavities of the heart. This would appear to be an important observation when considered in relation to the contentions of Parkinson, because it depicts clearly that a rapid dilatation of the heart can take place in a very short time even in the absence of active heart disease. If this increase in size of the heart can occur so quickly when there is no evidence of carditis, obviously dilatation may sometimes take place to the same degree in severely damaged hearts with slower rates. The second case showed, however, that moderate tachycardia, with a rate of 140 to 150, can occur at intervals over a long period without any appreciable effect on the size or shape of the heart when there is no active cardiac disease. When the myocardium is affected by an active disease process the problem assumes many other aspects, but it should be pointed out that, considering a large number of cases of heart disease in review, it is surprising how infrequently one finds a very rapid increase or diminution in the size of the cardiac shadow.

SUMMARY

Two cases of paroxysmal tachycardia in children showing no evidence of active heart disease are presented. In the first case rapid dilatation of the heart was shown to occur. In the second case the tachycardia was due to an ectopic focus in the auricle. The heart beat varied in its origin, being propagated from the ectopic focus at some times and from the sinus node at others.

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# HEREDITARY EPIDERMOLYSIS BULLOSA

## REPORT OF A CASE WITH A RÉSUMÉ OF THE LITERATURE

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With a few exceptions the papers and case reports dealing with epidermolysis bullosa have appeared solely in the dermatologic literature of Europe and America. Little has been written about the condition in the pediatric journals, particularly in this country. For this reason it seems worth while to report a case recently under observation in which the condition was present at birth, progressed rapidly and resulted in death after twenty-nine days.

### REVIEW OF THE LITERATURE

Beatty,[1] in 1897, published a résumé of all the cases of epidermolysis bullosa reported up to that date and added 3 cases of his own. He ascribed the first typical description of the disease to Goldscheider,[2] in 1882, but cited 2 cases recorded by Fox[3] in 1879 under the caption "Notes on Unusual or Rare Forms of Skin Disease: IV. Congenital Ulceration of the Skin (Two Cases) with Pemphigus Eruption and Arrest of Development Generally." In both these cases the patients' sisters, aged 6 and 2¼ years, respectively, had been born with the disease and showed typical lesions of what is now known as the dystrophic form of hereditary epidermolysis bullosa: i. e., widespread distribution of bullae, particularly on the exposed extensor surfaces; tendency of the bullae to become hemorrhagic; involvement of the tongue and of the buccal mucous membranes; loss of finger nails and toe nails; deformation of hands from scarring, and atrophy and thickening of the skin.

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From the Department of Diseases of Children of the College of Physicians and Surgeons, Columbia University, the Babies' Hospital and the Sloane Hospital for Women.

1. Beatty, W.: Epidermolysis Bullosa, Brit. J. Dermat. **9**:301, 1897.

2. Goldscheider, A.: Hereditäre Neigung zur Blasenbildung, Monatsh. f. prakt. Dermat. **1**:163, 1882.

3. Fox, T.: Notes on Unusual or Rare Forms of Skin Disease: IV. Congenital Ulceration of the Skin (Two Cases) with Pemphigus Eruption and Arrest of Development Generally, Lancet **1**:766, 1879.

Luithlen,[4] in 1902, gave a comprehensive review of the subject up to that time, together with excellent descriptions of the two generally recognized types of the disease, the simple and the dystrophic. These descriptions may be summarized briefly as follows:

In the simple form the bullae appear on the skin after mechanical irritation or slight trauma. The disease is usually congenital; the lesions may be present at birth or may appear first from a few days to two or three years after birth. The mucous membranes are not affected, and the nails are not involved. The blebs heal without leaving scars, and there is no permanent alteration in the skin. The general health of the patient remains unaffected, although the disease may persist indefinitely. In some cases the tendency toward the formation of bullae ceases at a later age, often at puberty.

In the dystrophic form the hereditary nature of the disease is present but is not as pronounced as in the simple form. The condition usually persists through life. The bullae appear at or soon after birth, as in the first form, and arise after trauma. They are more apt to become hemorrhagic. In healing, crusts and scabs are formed, resulting in permanent pigmentation and scarring. Occasionally deep ulcerations occur, but usually the skin shows atrophy, wrinkling or a xerodermatic condition. The skin may be thickened and crusted, especially over the knees and elbows. Thickening may be due, also, to horny cysts embedded in the skin. These resemble milia and either are scattered over the surface or appear in circumscribed groups. The cysts may disappear spontaneously after several weeks, or they may persist indefinitely. Itching may precede the formation of bullae or may be absent. Extensive degeneration of the nails is a constant characteristic of this type. The nails may be absent at birth or be shed soon afterward. When present they are always thickened and deformed, lamellated and without luster. The buccal mucosa and the tongue show bullae, ulceration, and leukoplakia, and there may be scarring of the lips. The tongue may be atrophic.

The observations of different investigators on the pathogenesis of hereditary epidermolysis bullosa show considerable variation and contradiction. That there are a more or less constant reduction and degeneration of the elastic tissue of the skin is pretty well agreed. Practically all investigators believe also that the bullae may be ascribed to a modified susceptibility or reactivity of the skin to injury, to an increased irritability of the integument which under normal conditions would result only in transient hyperemia. Some observers (Elliot,[5] Unna,[6]

4. Luithlen, F.: Epidermolysis bullosa hereditaria, in Mraček, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1902, vol. 1, p. 738.

5. Elliot, G. T.: A Further Contribution to the Histopathology of Epidermolysis Bullosa (Hereditaria), New York M. J. **71**:585 and 625, 1900.

6. Unna, P. G.: Ueber die Duhringsche Krankheit und eine neue Form derselben, Dermat. Wchnschr. **9**:97, 1889.

Török [7]) expressed the opinion that there is a congenital irritability of the vascular system of the skin, with the result that the basal portion of the rete is bathed in a serous transudate, undergoes degenerative changes and finally becomes detached from the connective tissue. Others, particularly Engman and Mook,[8] ascribed the formation of bullae to congenital absence of or defect in the elastic tissue of the papillary and subpapillary layers of the skin, with edema of the succulent horny layer and colliquation of many cells in the basal layers of the epidermis. These authors regarded the absence of elastic tissue as a primary phenomenon, while Beck,[9] and others stated the belief that the disappearance of elastic tissue results from degeneration, which in turn is provoked by persistent edema of the upper part of the corium.

Wise and Lautman,[10] in 1915, gave an excellent discussion of the symptomatology and pathology of the disease, with a complete review of the literature and bibliography up to that date. These authors reported a case of epidermolysis bullosa in which the lesions did not appear until the patient reached the age of 40. From the literature they collected 15 cases in which the condition did not manifest itself until after the age of 3 years. In 7 of these the onset occurred before puberty; in the remainder the condition appeared at ages ranging from 14 to 73 years and persisted throughout life. Wise and Lautman called the condition in this group of cases "acquired epidermolysis bullosa," stating that this term had first been employed by Karelitz [11] in 1904 in the title "Beitrag zur Frage der Epidermolysis bullosa (hereditaria et acquisita)."

Fordyce,[12] Elliot,[13] Le Blaye,[14] Fox,[15] Hallam [16] and MacKee [17] in various reports also stated that a noncongenital form probably exists.

7. Török, L.: Epidermolysis hereditaria bullosa (Koebner), Arch. f. Dermat. u. Syph. **47**:402, 1899.

8. Engman, M. F., and Mook, W. H.: A Study of Some Cases of Epidermolysis Bullosa, with Remarks upon the Congenital Absence of Elastic Tissue, J. Cutan. Dis. **24**:55, 1906.

9. Beck, S. C.: Beitrag zur Kenntnis der Epidermolysis bullosa, Virchows Arch. f. path. Anat. **213**:234, 1913.

10. Wise, F., and Lautman, M. F.: Epidermolysis Bullosa Beginning in Adult Life: The Acquired Form of the Disease, with the Report of a Case and Review of the Literature, J. Cutan. Dis. **33**:441 (June) 1915.

11. Karelitz, R.: Ein Beitrag zur Frage der Epidermolysis bullosa (hereditaria et acquisita), Inaug. Dissert., Rostock, 1904; cited by Wise and Lautman.[10]

12. Fordyce, J. A.: Pemphigus: A Case Demonstration, J. Cutan. Dis. **29**:549, 1911.

13. Elliot, G. T.: Two Cases of Epidermolysis Bullosa, J. Cutan. & Genito-Urin. Dis. **13**:10, 1895.

14. Le Blaye, R.: Pemphigus traumatique non congénital localisé sur les cicatrices, Ann. de dermat. et syph. **2**:178, 1911.

*(Footnotes continued on next page)*

Except for the fact that the onset is delayed beyond the third year, the acquired form is practically identical in its clinical manifestations, course and evolution with the congenital and hereditary forms. Its separation therefore, seems, hardly justifiable.

Finally, in 1934, in a long and detailed paper, Herlitz [18] described a new so-called lethal form of the disease which he termed "epidermolysis bullosa hereditaria letalis." He recognized the two main types previously described, i. e., the simple and the dystrophic form. Out of an extensive review of the literature, which was complicated by absence of uniform terminology and of strict criteria for diagnosis, Herlitz brought together 22 cases of the new form: 8 of his own, 3 of Mautner's,[19] 2 of Kuse's,[20] 7 of Jenny's [21] and 2 of Heinrichsbauer's.[22] The condition in the cases of this group differs from the classic simple and dystrophic forms in that it always leads to early death, which usually occurs before the third month. In no case was the duration longer than eight and one-half months. Herlitz's 8 cases occurred in three families, 4 in one of them, 2 in each of the others. In no instance had there been a previous case in any of the families, all of which came from the province of Uppland in Sweden and whose records went back to the beginning of the eighteenth century. The presence of extensive congenital cutaneous defects on the extremities was common. In the denuded areas the underlying structures, especially the tendons and blood vessels, were readily visible through the transparent tissue. The Nikolsky phenomenon (rubbing off of the skin in the bath) was present, but it was not possible to produce vesication by deliberate trauma, such as rubbing, pinching, or bandaging. There were marked dystrophy and deformity of the nails, some of which were absent at birth or fell off soon afterward. In some cases these lesions progressed to involve severe skeletal atrophy of the terminal phalanges. Histologically there

15. Fox, H.: Epidermolysis Bullosa, Acquired, J. Cutan. Dis. **33**:148, 1915.

16. Hallam, R., in Rolleston, H.: The British Encyclopedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 5, p. 82.

17. MacKee, G. M., and Cipollaro, A. C.: Skin Diseases in Children, New York, Paul B. Hoeber, Inc., 1936, p. 197.

18. Herlitz, G.: Kongenitaler, nicht syphilitischer Pemphigus: Eine Uebersicht nebst Beschreibung einer neuen Krankheitsform (Epidermolysis bullosa hereditaria letalis), Acta pædiat. **17**:315, 1935.

19. Mautner, H.: Ueber ein familiär auftretendes, letales Krankheitsbild mit Blasenbildung (Pemphigus hereditarius), Monatschr. f. Kinderh. **22**:15, 1922.

20. Kuse, K. H.: Ein Beitrag zum Krankheitsbild des Pemphigus hereditarius, Monatschr. f. Kinderh. **42**:513, 1929.

21. Jenny, E.: Ueber eine letal verlaufende Form von Epidermolysis bullosa hereditaria beim Saugling, Ztschr. f. Kinderh. **43**:138, 1927.

22. Heinrichsbauer, F.: Ein weiterer Beitrag zur Frage angeborener Hautdefekte (Ueber ein familiäres letales Krankheitsbild mit Blasenbildung und angeborenen Defekten der Haut), Arch. f. Gynäk. **134**:673, 1928.

was degeneration of elastic tissue, the skin was thinner than normal and the sweat glands and hair follicles were rudimentary. The author differentiated this condition from congenital syphilis and from congenital pemphigus neonatorum.

REPORT OF CASE

L. D., a white boy, was delivered spontaneously at term at the Sloane Hospital for Women. The weight at birth was 3,147 Gm. (6 pounds 15 ounces). The mother was a primipara, with a negative Wassermann reaction. There had been no miscarriages. No cutaneous lesions similar to those of this infant were present in any relative known to the parents. At birth there was an area almost encircling the infant's left wrist over which the epithelium was absent (fig. 1 *A*). The margins of this area were smooth and clear. There was no bleeding from the surface, which was transparent and clearly showed the deeper structures—tendons and blood vessels. Denuded areas were noted on the left thumb and on several fingers of the right hand (fig. 1 *B*). Ruptured vesicles with ragged, disintegrated epithelium were present at the tips of all the fingers. There was marked hyper-

Fig. 1.—*A*, circling defect of the skin of the left wrist at birth. *B*, ruptured bullae and dystrophic nails on the right hand at birth.

plasia of the nails, with paronychiae. Two of the finger nails were partially separated down to the matrix. The palms and soles were entirely clear, as was the skin of the remainder of the body.

*Course.*—Snuffles began on the second day. On the third day several bullae appeared on the legs spontaneously and on the arms at points of pressure where splints had been applied. On the fifth day bullae appeared in the mouth, in the pharynx and under the tongue. These quickly ruptured, leaving red macerated areas. On the thirteenth day new lesions appeared on the right toe, on the left elbow and the buttocks. The older lesions at this time were raw and oozing or crusted. They appeared infected and on culture yielded Staphylococcus aureus haemolyticus. Aseptic puncture of new bullae showed no organisms on smear or culture. During the third week the lesions spread to involve the entire body, with the exception of the palms, the soles and the scalp. On the twenty-third day (fig. 2) the left thumb nail fell off, followed by the nails of the first and second fingers of the right hand, those of the first and third fingers of the left hand and that of the left great toe.

Results of the physical examination remained negative throughout except for the cutaneous lesions. The lungs and the heart were clear. The spleen was not felt. The liver was felt 1 cm. below the costal margin.

The blood picture was normal throughout. The blood culture on the twenty-sixth day was negative. The Kahn reaction was negative. Cultures of unruptured bullae, as previously stated, were sterile, while those from old lesions showed Staphylococcus aureus haemolyticus, Staphylococcus albus haemolyticus and Bacillus proteus.

Biopsy of a newly formed bleb on the sixteenth day of life showed a thin layer of stratified squamous epithelium, five to ten cells deep, covered by a small amount of cornified epithelium. Adherent to the under surface was fibrin, embedded in the meshes of which were varying numbers of polymorphonuclears, eosinophils, round cells and erythrocytes. There were no bacteria in the exudate.

In spite of adequate caloric and fluid intake, the infant lost weight steadily and died on the twenty-ninth day.

*Necropsy.*—At necropsy gross examination showed extreme emaciation. Scattered over the entire body were numerous discrete and confluent lesions measuring from 1 mm. to several centimeters in diameter. These lesions were moist, bullous

Fig. 2.—Widespread distribution of lesions on the twenty-third day of life.

or crusted. The hands and feet were especially severely affected. The finger nails were barely distinguishable in the crusted, oozing digits. The great toe nail of the right foot had separated except at the base. The skin and the subcutaneous tissue were extremely thin, measuring 3 mm. in depth. The remainder of the gross examination gave negative results.

On microscopic section the specimens of skin showed no uniform picture, since practically all lesions were heavily infected, and varying degrees of inflammation and deep ulceration were predominating features. An occasional small vesicle lay entirely within the epidermis; the larger vesicles and bullae extended to the corium, and their cavities were partially filled with bacteria, coagulated fluid and degenerating cells. Beneath the deeper lesions bacteria had penetrated the corium, and the connective tissue was infiltrated with polymorphonuclear leukocytes and mononuclear cells, mainly of the myeloid type. In the ulcers bacteria were numerous, the superficial layer of the dermis had undergone necrosis, and in the adjacent connective tissue there were cells and edema. Variations in the elastic fiber content of the corium were discernible only in areas of necrosis or inflammation, where the absence of fibers or their apparent diminution in numbers could have been accounted for by local destruction or by the pushing apart of adjacent fibers by exudate. The sweat glands and hair follicles appeared normal.

COMMENT

This case seems definitely to belong to the small group described by Herlitz, which he called cases of "epidermolysis bullosa hereditaria letalis." The congenital cutaneous defect of the left wrist, the bullae on the right hand, the deformed, loosened nails at birth are typical of the disease. The subsequent involvement of the mucous membrane of the mouth, tongue and pharynx and the rapid and widespread formation of bullae, with secondary infection and constitutional debilitation resulting in early death are characteristic of the so-called lethal form of hereditary epidermolysis bullosa.

The cutaneous defect on the left wrist at birth is shown in figure 1 *A*, and a schematic comparison of this lesion with those described by Herlitz is shown in figure 3. Figure 1 *B* shows the ruptured bullae and

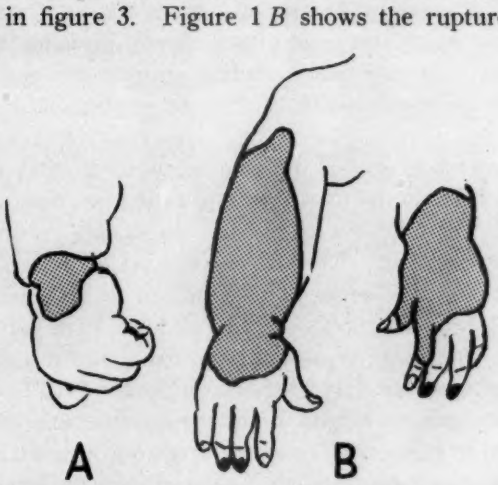


Fig. 3.—Schematic comparison of the cutaneous defect of the left wrist in the present case (*A*) with similar lesions (*B*) taken from Herlitz.[18]

dystrophic nails of the right hand at birth. Figure 2 gives a picture of the emaciation, the generalized and confluent nature of the lesions and the marked involvement of the nails on the twenty-third day of life, six days before death. Large areas over the posterior surfaces of the legs, the buttocks and the back were also involved. The buccal and pharyngeal mucous membranes were raw, bleeding and infected at this stage. Whether the extensive denudation of the body is solely responsible for the early termination or whether a constitutional abiotrophy underlying the superficial dystrophy of skin and nails is the main factor in the failure of such infants to survive is a matter of conjecture. It may well be that this type of the disease represents a general functional instability which in the simple and dystrophic forms is limited solely to the structures of the integument.

Because of the extensive microscopic changes found in the skin after death, many of which could be explained on the basis of the superimposed bacterial infection, it was impossible to draw definite conclusions as to the development of the initial cutaneous lesions. Conclusions as to the role of the elastic tissue were likewise impossible, because the absence or apparent diminution of elastic fibers might well have been accounted for by the secondary infection. Engman and Mook regarded this absence or diminution of elastic fibers as a primary structural defect, while the opinion of other observers held it to be secondary to degenerative changes in the basal portion of the rete, resulting in detachment of the rete from the connective tissue. This is still a moot point. Herlitz, who studied 6 of his 8 cases at autopsy, found the elastic tissue diminished in the denuded areas in 1 case; absent in the pars papillaris of the uninvolved skin in another, and of a dark and granular appearance in a third. Although he mentioned finding streptococci and staphylococci, he did not discuss their possible role in the production of the pathologic changes.

The differential diagnosis of bullous lesions at birth offers no great difficulty. Syphilis is the most common cause, but that disease shows a marked predilection for the palms and soles. The vesicles are always turbid, usually purulent. The base of the vesicle is infiltrated. Study of the serums of the mother and the infant is of great help. A few cases of varicella and variola occurring at birth have been recorded, but in every case the mother was suffering from the disease at the time. Pemphigus neonatorum may be fatal within the first few days of life; its identification may be helped by the presence of an epidemic. Culture of unruptured vesicles usually gives streptococci or staphylococci. In most cases the condition responds well to treatment, leaving no scars.

## SUMMARY

A résumé is given of the literature on epidermolysis bullosa hereditaria in its three principal forms, simple, dystrophic, and acquired, and in a new form recently described, epidermolysis bullosa hereditaria letalis.

A case is reported of an infant who died at the age of 29 days and who apparently had the so-called lethal form of the disease.

The differential diagnosis and the pathology of the disease are discussed.

# PROGERIA

## REPORT OF A CLASSIC CASE WITH A REVIEW OF THE LITERATURE SINCE 1929

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The term progeria, meaning prematurely old, was first given to a rare disease of childhood by Hastings Gilford.[1] The original case was described by Hutchinson,[2] but Gilford classified the disease as a distinct clinical entity and presented 2 cases of his own, in one of which the patient eventually came to autopsy The children all had many similar characteristics, notably, dwarfism, almost complete baldness, a beaked nose, a retracted chin, a narrow chest, prominent veins, arthritic changes, atrophy of the skin and subcutaneous tissues, obliteration of the normal depression of the umbilicus and peculiar brownish pigmented spots on the skin. In general the three patients presented some of the features of a young person, but these were combined with many of the stigmas of old age.

Reports in the American literature are few, and the first one, by Rand,[3] did not describe a typical picture of the disease. Curtin and Kotzen[4] in 1929 reported the case of a white girl of 7 years who died a few months after they first saw her from what appeared to be a true attack of coronary thrombosis. They reviewed the literature to 1929 and found only 10 cases of the rare disease progeria. Of these 10 cases, 4 were definitely atypical, namely, those of Rand, Schippers,[5]

1. Gilford, H.: Progeria: A Form of Senilism, Practitioner **73**:188 (Aug.) 1904.

2. Hutchinson, J.: Congenital Absence of Hair and Mammary Glands with Atrophic Condition of the Skin and Its Appendages, in a Boy Whose Mother Had Been Almost Wholly Bald from Alopecia Areata from the Age of Six, Med.-Chir. Tr. **69**:473, 1886.

3. Rand, C. W.: A Case of Supposed Progeria in a Girl of Eight Years, Boston M. & S. J. **171**:107 (July 16) 1904.

4. Curtin, V. T., and Kotzen, H. F.: Progeria: A Review of the Literature with Report of a Case, Am. J. Dis. Child. **38**:993 (Nov.) 1929.

5. Schippers, J. C.: A Case of Progeria, Nederl. tijdschr. v. geneesk. **2**: 2274 (Dec. 23) 1916.

Farran-Ridge [6] and Talbot.[7] Hence, with the case of Curtin and Kotzen reported in 1929, only 7 typical cases had been reported to that time.

We have reviewed the literature from that date to the present and have found a single additional report in the American literature. This was by Stern and Lieberman.[8] The child was less than 2 years old and presented some of the features of progeria, but she would have had to be followed longer for her condition to be definitely classed as such. There have been 11 reports in foreign journals in the last nine years, 6 of which are undoubtedly of classic cases, namely, those of Thiers and Nahan,[9] Barraud,[10] Schiff,[11] Broc and his associates,[12] Exchaquet [13] and Papek and Hadlik.[14]

The cases reported by Hallé and Odinet,[15] Pouzin-Malegue,[16] Martinez,[17] Heuyer and his co-workers [18] and Sundblad [19] are not typical and cannot be classed definitely as instances of progeria.

To these 13 classic cases we wish to add another, which resembles strikingly the cases reported by Gilford. In fact, the photographs of all patients with the classic form are so similar that even a casual observer would take any two of the children for twins (fig. 1).

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6. Farran-Ridge, C.: Note on a Case of Premature Senility, J. Neurol. & Psychopath. **2**:254 (Nov.) 1921.

7. Talbot, F.: Metabolic Study of a Case Simulating Premature Senility, Monatschr. f. Kinderh. **15**:643 (March) 1923.

8. Stern, A., and Lieberman, D. P.: Supposed Progeria in a Girl Aged Seventeen Months, Arch. Pediat. **54**:169 (March) 1937.

9. Thiers, J., and Nahan: Roentgenologic Study of the Skeleton in a Case of Gilford's Progeria, J. de radiol. et d'électrol. **17**:675 (Dec.) 1933.

10. Barraud, G.: Senile Dwarfism or Progeria, Gaz. méd. de France, Nov. 15, 1934, p. 983.

11. Schiff, E.: Progeria: Dwarfism of the Senile Type, Schweiz. med. Wchnschr. **64**:213 (March 10) 1934.

12. Broc, R.; Nicolle, M., and De Beaujeau, A. V.: Progeria: Study of Lesions of the Bony Structure, Presse méd. **43**:786 (May 15) 1935.

13. Exchaquet, L.: A Case of Progeria, Rev. méd. de la Suisse Rom. **55**:248 (March 25) 1935.

14. Papek, J., and Hadlik, J.: Progeria or Senile Nanism, Časop. lék. česk. **77**:11 (Jan. 7); 58 (Jan. 14); 81 (Jan. 21) 1938.

15. Hallé, J., and Odinet, J.: Absence of Hair and Malformations: Possible Similarity to Progeria, Bull. Soc. de pédiat. de Paris **30**:327 (May) 1932.

16. Pouzin-Malegue, Y.: A Case of Senile Dwarfism or Progeria, Bull. Soc. de pédiat. de Paris **30**:685 (Dec.) 1932.

17. Martinez, C. H.: Study of a Case of Progeria, Crón. méd., Lima **52**: 372 (Oct.) 1935.

18. Heuyer, G.; Denoyelle, L., and Bernard, A.: Dwarfism with Infantilism, Microcephaly, Osseous and Cutaneous Abnormalities Similar to Senile Dwarfism or Progeria, Bull. Soc. de pédiat. de Paris **34**:159 (March) 1936.

19. Sundblad, R.: Gilford's Progeria Due to Syphilitic Dystrophy, Arch. argent. de pediat. **6**:624 (June) 1938.

REPORT OF CASE

*History.*—A white girl of 10 years was first seen on May 13, 1937. She was brought in for a general examination and because she seemed never to have grown properly since she was dropped on her head when 13 months old. She had two sisters, one 18 years old and the other 5 years old, who were normal. She weighed 8½ pounds (3,855 Gm.) at birth. There were no convulsions or cyanosis at this time. She received cod liver oil and orange juice in infancy and was breast fed for about one year. She cut her first tooth at the age of 5 months, sat up alone at 6 months and walked and said a few words at 11 months. She had

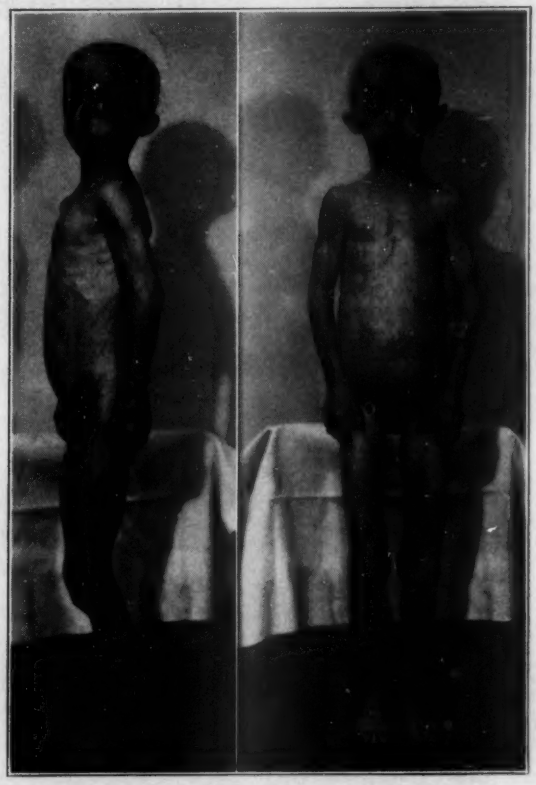

Fig. 1.—Ten year old girl with progeria. Note the bald head, beaked nose, retracted chin, narrow upper part of the chest, protruding abdomen with obliteration of the umbilicus, pigmented spots over the abdomen, prominent veins and arthritic changes which are especially evident in the hands and knees.

pertussis at the age of 3 years and mumps at 3½ years. During her second year she lost all her baby hair. However, the parents were not conscious of the fact that she was definitely abnormal until she reached the age of 3 years. At this time she began to lose weight. They realized that her stature was shorter than it should be and that she had not grown for some time. They could not tell with any reasonable degree of accuracy when most of the changes first occurred. These were gradual, and she had grown progressively worse. Her weight had

been stationary for the past two years. Her appetite was tremendous and had been so for about twelve months. The parents thought that she ate almost as much as an adult. She was abnormally sensitive to heat and cold. She had always been alert mentally. She went to school for the first time at the age of 8 years and remained in school only four and one-half months. Her penmanship was good, and she enjoyed writing letters and mailing them. She liked to read the "funnies" and children's books. She was particularly good in arithmetic. She liked to play with other children and was especially fond of babies. She did not prefer the company of adults. She rarely cried except when her younger sister was hurt. She played hard but tired easily. She was fond of animals and was much disturbed when she lost any of her pets. She liked to play with dolls, and her mother thought that her activities were those of a normal child of her years. She was not at all sensitive when her condition was talked about in her presence. She realized that she was different from other children and had probably realized it for the past five years. She seemed to enjoy life and would have lived at the movies if her parents had let her. She liked music and listened to the radio a great deal. She had a lovely voice and sang a popular song for us at her parents' request. Paradoxically, the one chosen was "Little Old Lady."

*Physical Examination.*—The patient weighed 28 pounds 2½ ounces (12.77 Kg.), and her height was only 41½ inches (105.4 cm.). The blood pressure was 136 systolic and 86 diastolic and the pulse rate 130 per minute. The head was almost bald and was abnormally large in comparison with the size of the face. The impression one got in looking at her was that of a plucked bird. There were a few fine grayish blond hairs, about 1 inch long, scattered over the parieto-occipital region of the scalp. The frontal and parietal bosses were unduly prominent. The fontanels were closed, and the head appeared hydrocephalic, measuring 19 inches (48.2 cm.) in circumference. The ears were small, lacked normal lobules and protruded from the head almost at right angles. The drums were normal. The skin of the scalp and face was not wrinkled but was thin and tightly drawn over the subcutaneous tissues. There were no eyebrows, but there were sparse, short blond eyelashes. The eyes appeared to protrude somewhat, but the apparent exophthalmos was due to the marked atrophy of the facial subcutaneous tissue. The pupils were equal and reacted normally to light and in accommodation. There was no strabismus or nystagmus. Extraocular movements were unimpaired. The nose was small and beaked like that of a bird, probably because of atrophy or lack of development of the nasal cartilages. The fat pads of the face were still present. The chin was markedly retracted and the submaxillary glands on both sides were prominent, which made the child look as though she had a double chin. The skin of the neck was covered with fine brown pigmented spots. The thyroid gland was not palpable. There were four very carious deciduous teeth. Only one permanent tooth had erupted. The throat was normal, although the palate was highly arched. The skin of the chest was pigmented, with small brown scattered spots. The unpigmented portion of the skin had a yellow cast. The chest was small in comparison with the abdomen. The ribs seemed to be atrophied but were unusually prominent. There was a slight funnel breast, and the ensiform cartilage was prominent. The clavicles appeared atrophied. There was marked loss of subcutaneous tissue over the chest, and the nipples were small and unpigmented. Expansion of the chest was somewhat limited on both sides. Breath sounds were normal throughout, and no rales were heard. The circumference of the chest at the nipple line was 18¾ inches (47.6 cm.).

The heart seemed slightly enlarged on percussion. The apex beat was prominent in the fourth and fifth interspaces 2½ inches from the midsternal line. No thrills or shocks were noted. There was a slight blowing untransmitted systolic murmur at the apex. The rate was rather rapid. The rhythm was normal, and the sounds were of good quality. The skin was more markedly pigmented on the abdomen than on any other portion of the body. The abdomen was protuberant, and the normal depression of the umbilicus was obliterated. The abdomen measured 19½ inches (49.5 cm.) at the umbilicus. The tip of the spleen was palpable on deep inspiration. No other organs or masses were palpable. There was a

Fig. 2.—Note the thickening of the cortex of both femurs, outward bowing of the shafts and elongation of the necks, which continue almost in a straight line with the shafts.

small xanthomatous plaque, about the size of a large pea, in the skin of the left lower quadrant of the abdomen. The external genitals seemed normal for a child of her age.

The extremities were similar to those of a wasted, gnarled old person. There was marked general wasting of muscles and subcutaneous tissue. The veins were unduly prominent. The deltoids and the muscle groups around the elbows appeared hypertrophied and gave the impression that muscular dystrophy was present. The hands were small, with marked atrophy of the interosseous muscles. The fingers were short, and arthritic changes were prominent in the bulbous

metacarpophalangeal joints. The nails were atrophied and furrowed and appeared very brittle. Nails were absent from the four small toes of each foot. The knees showed prominent arthritic changes and were partly flexed all the time. The feet were small, and the loss of subcutaneous tissue was marked. The superficial reflexes were bilaterally diminished. No abnormal reflexes were noted. The sensorium was normal.

*Laboratory Examination.*—Only a few laboratory tests were done, because of unwillingness on the part of the parents to subject the child to much discomfort. Her basal metabolic rate was —10 per cent. Two examinations of the urine gave negative results, and a blood count, done July 23, showed 80 per cent hemoglobin, 4,510,000 red blood cells and 9,800 white blood cells, with 59 per cent polymorphonuclears, 40 per cent lymphocytes and 1 per cent eosinophils. Wassermann and tuberculin tests gave negative results.

The roentgen examination, done by Dr. H. D. Gray, revealed that the skull was normal except that it had a thin wall and the coronal suture was not closed. The sella turcica was normal. The ribs, clavicles, scapulas, pelvis and lower part of the spine had developed normally, although the bones were small. The epiphyses at both ends of the humeri were prematurely united with the shafts. There were thickening of the cortex of both femurs, outward bowing of the shafts and elongation of the necks, which continued almost in a straight line with the shafts (fig. 2). This is a fairly constant finding in classic cases. The phalanges showed premature union of all epiphyses, and the distal phalanges were cone shaped and appeared smaller than normal.

## COMMENT

In attempting to discuss the etiology of this interesting morbid state we are truly groping in the dark, because of the extremely few patients who have come to autopsy. In spite of the marked similarity in the appearance of the patients in the classic cases reported in the literature, the evidence of glandular dysfunction varied widely in many of them. Exchaquet's patient had a blood calcium content of 15 mg. and marked decalcification of bone. The basal metabolic rate was markedly increased. On subsequent examination Exchaquet found atrophy of the clinoid processes of the sella turcica. From these findings he deduced that a basophilic secretory adenoma was present which caused an accelerated parathyroid and thyroid function. Pressure of the adenoma on the acidophilic cells of the hypophysis accounted for the deficiency in growth. However, atrophy of the sella turcica was not present in our case or in the other cases reported, and hypophysial tumor was not mentioned in the reports of cases in which autopsy was performed. Hence this cannot be accepted as the etiologic factor in all cases of progeria.

The patient of Thiers and Nahan had symmetric healed fractures of the upper end of both humeri and subtrochanteric fractures of both femurs. The patient of Broc and his associates showed marked demineralization of bone with changes that looked like osteitis fibrosa cystica. In spite of the fact that an excess of parathyroid secretion apparently plays a part in the bony changes which are present in some cases, the

many other changes of both dwarfism and senility cannot possibly be explained except by a pluriglandular process. Perhaps Nasso [20] was right when he said that there is an absolute incapacity of the organism to develop, with a deterioration of the endocrine glands and other organs and tissues, causing a rapidly developing premature old age. An autopsy on one of Gilford's patients showed marked atheromatous changes in the aorta blocking the coronary arteries, which may add weight to Nasso's statement. The patient of Papek and Hadlik had an extremely bad family history. The child's mother had active tuberculosis with high fever in the eighth month of her pregnancy. The authors attributed the development of the child's many evidences of glandular dysfunction, some of which were present at birth, to this fact. Schiff offered no explanation for the development of the condition in his patient, nor can we shed any light on it.

SUMMARY

A classic case of progeria is reported. From our review of the literature we feel that it is the fourteenth typical case recorded. The pictures of all patients with this disease are so similar that we must assume that they are siblings under the skin. The cause of this rare morbid state is still unknown and the treatment entirely empirical.

1073 Madison Avenue.
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20. Nasso, I.: Clinical Contribution to the Study of Progeria, Pediatria **33:** 1213 (Nov. 15) 1925.

# DIABETES MELLITUS IN ONE OF IDENTICAL TWINS

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The purpose of this report is to record the occurrence of diabetes mellitus in one of identical twins, the growth and development of both twins and dextrose tolerance studies of the nondiabetic twin. Because diabetes is rare in twins, especially in childhood, the opportunity to study a nondiabetic twin seldom presents itself. The present study is the first of this type to be described in the literature.

## REPORT OF A CASE

Mildred and Helen S. were born at the Bronx Hospital June 20, 1930. The first child, Mildred, was born at 7: 50 a. m., by vertex presentation, weighing 5 pounds 4 ounces (2,381 Gm.). A second sac was then found. This was ruptured, and the second child, Helen, was delivered by breech extraction ten minutes later. Her birth weight was 5 pounds 9 ounces (2,523 Gm.). Only one placenta was delivered. The children developed normally until the age of 3 years and 9 months, when they had moderately severe measles. Shortly thereafter Mildred became irritable and lost 5 pounds (2,268 Gm.) and polyuria and polydipsia developed. Urinalysis revealed glycosuria. She was admitted to Mount Sinai Hospital in May 1934. The diagnosis of diabetes mellitus was corroborated by a blood sugar content during fasting of 300 mg. per hundred cubic centimeters and the presence of 5 per cent of a reducing substance in the urine which chemically and polariscopically was proved to be dextrose. Mildred's diabetes was controlled, and she left the hospital in June 1934 on a diet of carbohydrates 85 Gm., protein 50 Gm. and fat 90 Gm. (total calories, 1,350) with 7 units of insulin before breakfast and 5 units before her evening meal (fig. 1).

The twins have been seen every month or two since that time. They are at the time of writing 8½ years old. Because their habits were so much alike, it was realized that psychologically it would be difficult to feed one child larger amounts of food than the other. They were therefore given the same diet, which gradually has been increased until each child now receives approximately 140 Gm. of carbohydrates, 70 Gm. of protein and 100 Gm. of fat (total calories, 1,740). Mildred's condition is at present well controlled with a single injection of 24 units of protamine zinc insulin. The twins occasionally exceed their prescribed diets, particularly Helen, the nondiabetic child. The self control of both children, however, is admirable, although, as so often occurs, the taste for sweets is lost when the habit of eating them is curtailed.

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From the Children's Diabetic Clinic, Department of Pediatrics, Mount Sinai Hospital.

Each child lost her first tooth at the age of 5 years, and eruption of the permanent central incisors followed immediately. The first permanent molar appeared in each child just before the sixth birthday. The twins are in the same class at school, do good work and seem to have about the same degree of intelligence. Each has had a few minor infections of the respiratory tract. Both had severe pertussis in June 1938; Mildred's carbohydrate tolerance was not disturbed. Each child lost some weight but soon regained it. In February 1939 they had varicella, which temporarily aggravated Mildred's diabetes. She required additional regular insulin for a short time and then regained her usual tolerance. Helen remained nondiabetic.

The development of both children has been carefully followed. Except for the temporary loss of weight at the onset of Mildred's

Fig. 1.—Mildred and Helen at the age of 4 years, soon after Mildred's diabetes was discovered.

diabetes, their weights have been approximately the same (fig. 2). This demonstrates a fact which has been noted repeatedly in the children's diabetic clinic, namely, that diabetic children are as heavy or heavier than normal children of the same age in spite of their somewhat lower caloric intake. The extra weight may be the result of water retention due to continued use of insulin.

The children were the same height when Mildred's diabetes began (fig. 3). The nondiabetic child is now about 3 cm. taller than her sister. The most probable explanation for this is that because of glycosuria the diabetic child metabolizes fewer calories than her sister with a similar

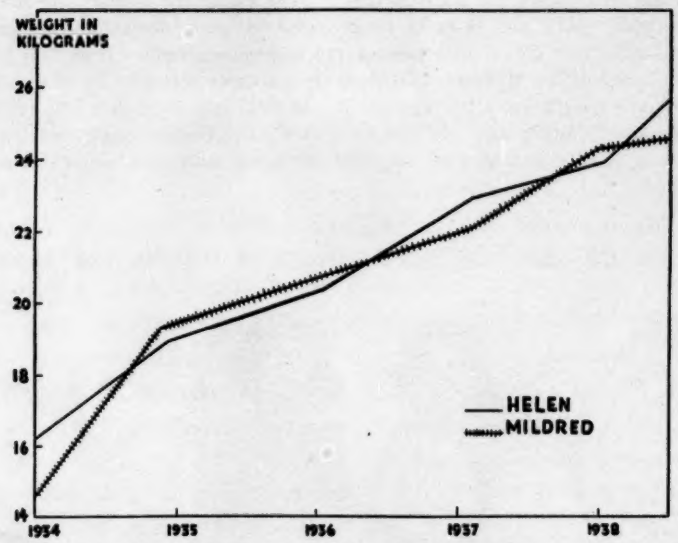


Fig. 2.—Comparison of weights of Mildred and Helen from 1934 to 1938.

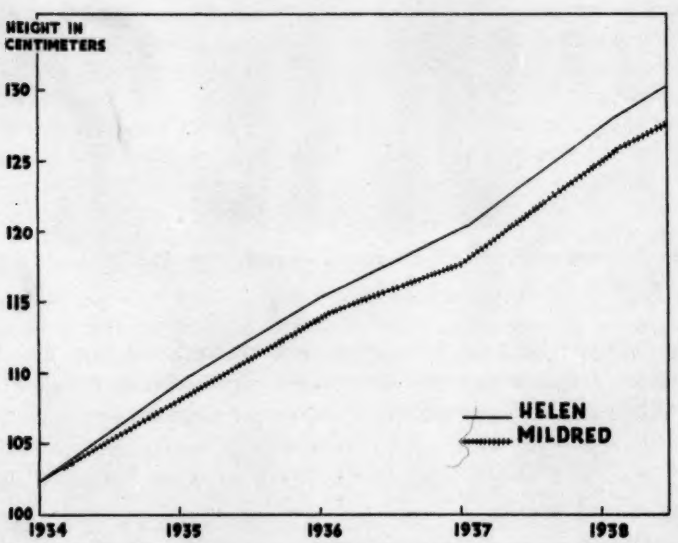


Fig. 3.—Comparison of heights of Mildred and Helen from 1934 to 1938.

caloric intake. Mildred's shorter stature may also be the result of restricted muscular activity, because, being diabetic, she has less energy and is not as active as her sister.

### PROOF THAT THE TWINS ARE IDENTICAL

A number of facts have been gathered in order to prove that these children are identical twins:

*Sex.*—Both children are females. It is self understood that identical twins must be of the same sex.

*Sacs and Placentas.*—There were two amniotic sacs with one placenta according to the obstetrician's report. Single ovum twins are almost always attached to one placenta, although occasionally they may have separate placentas if fission occurred in the morula stage. Double ovum twins, on the other hand, usually have separate placentas, although these may fuse. Therefore a diagnosis of single or double ovum twins can often, but not invariably, be made from the number of sacs and placentas.[1]

*Size of Fetus.*—The birth weights were 5 pounds 4 ounces (2,381 Gm.) and 5 pounds 9 ounces (2,523 Gm.). The weights of newborn identical twins may vary, depending on differences in the intra-uterine blood supply. Double ovum twins are apt to vary considerably more in their birth weights.

*Color of Hair and Eyes.*—Each child has light brown hair and gray eyes. Single ovum twins must have the same color hair and eyes.

*General Appearance.*—The faces and expressions of identical twins are much alike, usually from birth. The similarity often becomes more marked during later childhood (fig. 4).

*Mental Characteristics.*—Disposition and talents are apt to be alike. Mildred and Helen are both serious and introspective.

*Fingerprints.*—Fingerprints of the twins were made by Mr. L. L. Tuck of the police department of the city of New York. These were reported as "showing similar patterns and in most respects very much alike." Since no two persons have identical fingerprints, the unusual similarity between Mildred's and Helen's tracings is significant. It is unlikely that nonidentical twins would have such similar prints.

*Blood Groups.*—While nonidentical twins may or may not have blood of the same group, identical twins always do. The blood of the two children is serologically identical and belongs to group O; it contains

1. De Lee, J. B.: Principles and Practice of Obstetrics, ed. 7, Philadelphia, W. B. Saunders Company, 1938, p. 535.

the hereditary blood factors M and N.[2] Schiff and von Verschuer[3] have shown that the blood of 75 per cent of nonidentical twins differs when compared as to these serologic qualities. The similarity of the blood of these children is therefore additional evidence that they are identical twins.

It may therefore be said that all the available evidence substantiates the premise that Mildred and Helen are identical twins.

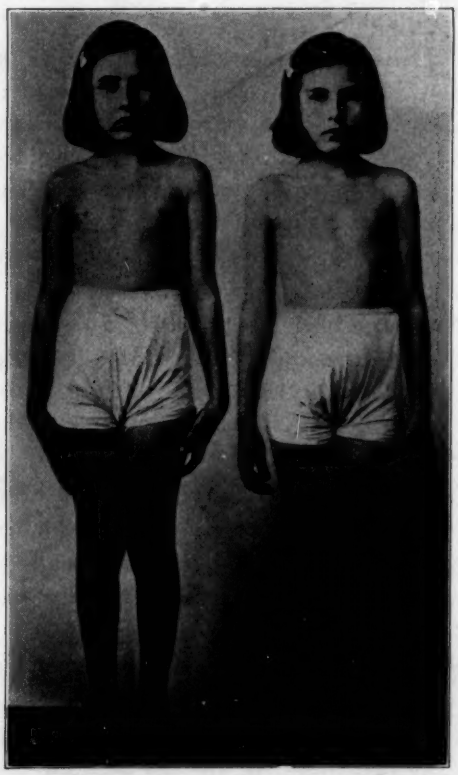

Fig. 4.—Mildred and Helen at the age of 8½ years.

## COMMENT

The force of heredity is perhaps nowhere more clearly shown than in the occurrence, sometimes almost simultaneous, of diabetes in the two members of a pair of identical twins. The greater incidence of diabetes

2. Dr. Fritz Schiff, bacteriologist of Beth Israel Hospital, examined the blood.

3. Schiff, F., and von Verschuer, O.: Serologische Untersuchungen an Zwillingen, Ztschr. f. Morphol. u. Anthropol. **32**:244, 1933.

in relatives of diabetic persons than in a control population is additional evidence that diabetes is an inheritable disease.[4]

Joslin [5] has reported diabetes mellitus in members of 16 pairs of similar and 19 pairs of dissimilar twins. Diabetes occurred in both members in 11 of the 16 sets of similar twins but in only 2 of the 19 sets of dissimilar twins. It is noteworthy that diabetes occurred so much more often in both members among similar twins than among dissimilar ones. Curtis [6] collected the cases of diabetes mellitus in twins to 1929. Since then a few more instances, in all of which the twins were adults, have been recorded.[7] The age of onset of childhood diabetes in similar twins which Joslin tabulated was 2 and 3 years in one pair, 5 and 8 years in another pair and 3 and 13 years in the third pair. The figures for twins of course are not complete, for they exclude pairs in which one member died in infancy or early childhood from a cause other than diabetes. Nor can they include pairs in which diabetes may develop in the future.

Joslin and his associates [8] have also noted relative hyperglycemia in families of diabetic patients as compared with the control population and have concluded that these persons are potentially diabetic. My associates and I have been interested in this problem for some time and have published a series of dextrose tolerance curves of siblings of the diabetic children under our care.[9] We found practically no abnormal dextrose tolerance curves which were confirmed by a second test. Such studies are of course not conclusive, for they demonstrate the dextrose tolerance only at certain hours of a given day. Moreover, the type of curve depends to some extent on the composition of the previous day's diet. In the six years since these studies were made, none of the children whom we tested has shown evidence of diabetes.

Nevertheless, from what has been said of the concurrence of diabetes in similar twins, one might expect that Helen, the nondiabetic twin, would show a decreased tolerance for dextrose. She was studied three

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4. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: V. Heredity, Am. J. M. Sc. **193**:8 (Jan.) 1937.

5. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1938, pp. 49-50.

6. Curtis, W. S.: Diabetes in Twins, J. A. M. A. **92**:952 (March 23) 1929.

7. Peck, F. B.: Diabetes in Twins, J. Michigan M. Soc. **32**:359 (June) 1933. Umber, cited in Emigration of Physicians from Germany in 1933, Foreign Letters (Berlin), J. A. M. A. **102**:1242 (April 14) 1934. Watson, E. M.: Diabetes Mellitus in Twins, Canad. M. A. J. **31**:61 (July) 1934.

8. White, P.; Joslin, E. P., and Pincus, G.: The Inheritance of Diabetes, J. A. M. A. **103**:105 (July 14) 1934.

9. Mackler, H. S., and Fischer, A. E.: The Sugar Tolerance in Siblings of Juvenile Diabetic Patients, J. A. M. A. **103**:240 (July 28) 1934.

times (fig. 5). The first curve was obtained soon after Mildred's diabetes developed. The second was made in 1935, shortly after an infection, and apparently showed a decreased tolerance for dextrose. This might have signified impending diabetes. However, the urine on repeated examination showed no dextrose. The last curve, made in November 1938, was normal. One can therefore say that, although statistics indicate the probability that Helen will acquire diabetes, there is no indication of it other than the single high dextrose tolerance curve in 1935. It is my impression that the dextrose tolerance curve for the blood may not be as indicative of a potential breakdown in normal carbohydrate metabolism in children as it is in adults, for the onset of diabetes in children usually occurs much more suddenly. Temporary disturbances may follow an infection, as demonstrated by Kohn

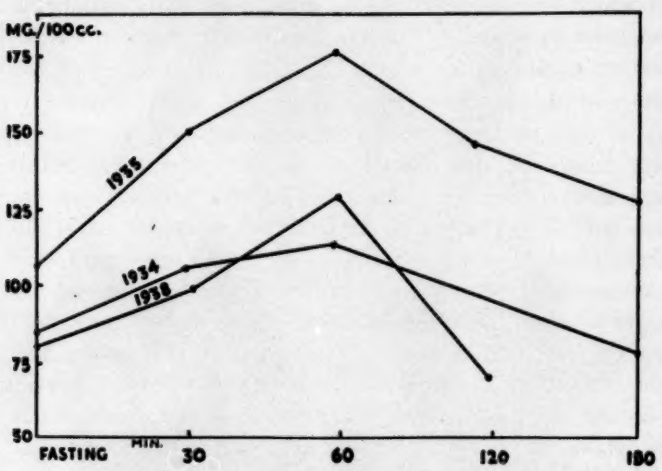


Fig. 5.—Dextrose tolerance curves for Helen.

and Felshin [10] and by Williams and Dick.[11] However, since the children who show such decreases in tolerance rarely become diabetic, their curves should be considered only as indicating temporary disturbances in dextrose metabolism due to infection.

Curtis [8] spoke of protecting siblings, especially identical twins, against diabetes by restricting their diet. However, diabetes may develop regardless of diet in a person whom heredity has made susceptible. Such a person may become diabetic because of an infection which upsets a potentially defective dextrose metabolism. It is there-

10. Kohn, J. L., and Felshin, G.: Dextrose Tolerance Tests Following Lobar Pneumonia in Children, Am. J. Dis. Child. **39**:512 (March) 1930.

11. Williams, J. L., and Dick, G. F.: Decreased Sugar Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.) 1932.

fore possible that Helen, the identical twin of a person with diabetes, may eventually have diabetes. There is as yet no indication of it from the studies which have been made of her tolerance for dextrose.

SUMMARY

A case of diabetes mellitus in one member of a pair of identical twins is reported.

Height and weight curves for both twins are given.

Proof that the children are identical twins is established.

The nondiabetic twin has been studied and has been found to have a normal tolerance for dextrose.

The nondiabetic twin has not shown evidence of diabetes mellitus as yet, although her heredity suggests the likelihood of its development later in life.

# Abstracts from Current Literature

## Anatomy and Physiology

THE SPINAL ACCESSORY NERVE IN HUMAN EMBRYOS. A. A. PEARSON, J. Comp. Neurol. **68**:243 (Feb.) 1938.

For this study of the spinal accessory nerve of the human embryo, 7 embryos, measuring between 19 and 70 mm., crown-rump length, were available, prepared either by the activated protein silver or the pyridine silver method. Preparations stained with toluidine blue and with hematoxylin were also studied. The cells of origin of the spinal portion of the accessory nerve formed a cell column from the region of the junction of the spinal cord with the medulla oblongata into the sixth cervical segment. The intraspinal course of the accessory rootlets was variable, as was the course of the spinal accessory trunk within the vertebral canal. Usually the trunk passed through the ganglion of the first cervical nerve. Ganglion cells observed along the course of the accessory nerve suggested to Pearson the presence of a sensory component.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

## Biochemistry; Bacteriology, and Pathology

PHLORHIZIN GLYCOSURIA AND HYPOGLYCEMIA UNAFFECTED BY EXCESS INGESTION OF NA AND K SALTS. M. ZIEGLER and I. MCQUARRIE, Proc. Soc. Exper. Biol. & Med. **39**:142 (Oct.) 1938.

In order to determine whether or not carbohydrate metabolism in phlorhizinized animals is influenced by ingestion of excessive amounts of sodium and potassium salts as it is in normal and diabetic subjects, 4 dogs phlorhizinized by daily subcutaneous injections of 100 mg. of phlorhizin per kilogram of body weight were fed comparatively large amounts of these salts. Two animals received sodium chloride amounting to 1 Gm. per kilogram per day. Two were given potassium chloride, one of these receiving 1 Gm., the other 0.5 Gm., per kilogram per day. The excretion of dextrose, minerals and nitrogen was determined during the following six or seven day periods: a foreperiod, a period of ingestion of salt, a period of administration of phlorhizin and a period of ingestion of phlorhizin plus salt. In addition, the sugar, nonprotein nitrogen and electrolytes of the blood were determined at appropriate intervals. The degrees of hypoglycemia and of glycosuria resulting from the administration of phlorhizin were not significantly influenced by the ingestion of either salt. The decrease in serum potassium due to phlorhizin was somewhat accentuated by ingestion of sodium, but no other effects were noted. It is concluded that the phlorhizinized animal does not respond like the diabetic subject to the ingestion of sodium and potassium salts.

HANSEN, Minneapolis.

SEROLOGIC TYPES OF SALMONELLA ISOLATED FROM PARATYPHOID IN CHICKS. E. JUNGHERR and C. F. CLANCY, J. Infect. Dis. **64**:1 (Jan.-Feb.) 1939.

These authors studied Salmonella in fowl with the intent to shed some light on the epidemiologic relationships of human and animal paratyphoid. In the examination of 1,241 chicks less than 3 weeks old they found 15 with paratyphoid infection, 470 with Salmonella pullorum disease and 756 with disease the Salmonella nature of which was not established. Although the symptoms were not definite, the pathologic lesions at autopsy ranged from minor alterations to omphalitis, peritonitis, pericarditis and sacculitis and occasionally tumefaction and focal necrosis of the liver. It was stated that the navel appeared to be the portal of entry. From an

epidemiologic standpoint it was interesting that 10 of the 15 infected birds were observed in what is known as pullorum-clean stock. A review of the literature reveals that all of the Salmonella types save one, Salmonella anatum, observed in chicks were found associated with gastrointestinal disturbances in man.

TOOMEY, Cleveland.

EFFECT OF SULFANILAMIDE ON PNEUMOCOCCAL INFECTIONS IN MICE. J. M. RUEGSEGGER and M. HAMBURGER, J. Infect. Dis. **64**:18 (Jan.-Feb.) 1939.

Sulfanilamide administered parenterally tends to prolong the lives of mice inoculated with virulent strains of Pneumococcus types 1, II, III and VIII. No protective action was apparent in this serie of experiments. Studies were not made on the exudates in an attempt to learn the mode of action of the drug. Sulfanilamide has little toxicity for the white mouse except when given in large doses.

TOOMEY, Cleveland.

EFFECT OF SULFANILAMIDE THERAPY UPON BOVINE MASTITIS AS INDICATED BY LABORATORY TESTS. W. G. HOGE, W. V. HALVERSEN and V. A. CHERRINGTON, J. Infect. Dis. **64**:27 (Jan.-Feb.) 1939.

Detailed data were compiled showing the effect of sulfanilamide therapy on bovine mastitis. Blood agar plate counts and breed smears were made from the milk from each quarter of 5 experimental animals to determine the effect of the medication on the disease. The concentrations of sulfanilamide in the blood, milk and urine of the cows were determined to establish any relationship between the amount present in the body fluids and the effect produced on the condition of the udder. The case histories of the cows receiving the therapy are given, and a short qualitative experiment showing the in vitro effect of sulfanilamide on organisms associated with mastitis is described.

The cows tested tolerated doses of 5 Gm. per hundred pounds (45.5 Kg.) of body weight per day (the dose often prescribed in human infections). In some cases this dose was doubled without producing serious symptoms of toxicity. Uniform concentrations of the drug in blood and milk were well maintained by only two or three daily doses.

The counts of bacteria in the milk were much reduced during medication in all cases, and in most cases the milk was temporarily rendered nearly or completely sterile by the drug. Improvement in the clinical picture and in the milk was noted in 1 case in which acute mastitis was treated. There was no permanent improvement in the udder as revealed by the bacteriologic examination of the milk or by the leukocyte count in any of the cases studied.

No positive general statement can be made as to the effect of sulfanilamide on the number of leukocytes in the milk of treated cows. These experiments indicate that there is probably a decrease in numbers.

Sulfanilamide in litmus milk cultures of organisms associated with mastitis markedly inhibits the action of the organisms on the milk. The effect of the drug appears to be much greater in vivo than in vitro.

TOOMEY, Cleveland.

EFFECT OF SULFANILAMIDE ON EXPERIMENTAL INFECTIONS WITH BACTERIUM NECROPHORUM IN RABBITS. E. S. HEMMENS and G. M. DACK, J. Infect. Dis. **64**:43 (Jan.-Feb.) 1939.

Sulfanilamide was used in rabbits infected with Bacterium necrophorum. "In order to get maximum effect and ultimate cure it was necessary to start treatment by the third day of the infection or earlier and to continue treatment until the lesion had regressed. The effect of the drug was to stop the spread of the necrotic process. Histologically, there was a connective tissue wall infiltrated with heterophil leukocytes in the animal treated for four days or longer. This process went on to complete encapsulation if treatment was continued.

"There were fewer bacteria in the abscess of the treated as compared with the untreated animal.

"The mode of spread of the infection seemed to be through the blood vessels."

TOOMEY, Cleveland.

ACTION OF PRONTOSIL-SOLUBLE AND SULFANILAMIDE ON THE PHAGOCYTIC ACTIVITY OF LEUKOCYTES AND ON THE DISSOCIATION OF STREPTOCOCCI. R. TUNNICLIFF, J. Infect. Dis. **64**:59 (Jan.-Feb.) 1939.

Tunnicliff shows that prontosil-soluble (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate, now known as neoprontosil) in high dilutions, 1:1,000 to 1:1,000,000, and sulfanilamide diluted 1:100,000 to 1:2,000,000 in salt solution promote phagocytosis of alpha and beta streptococci apparently by stimulating the activity of leukocytes. They have no effect on opsonins. Both drugs were injected subcutaneously into mice, and they appeared to stimulate the activity of the leukocytes to the same degree. TOOMEY, Cleveland.

USE OF SULFANILAMIDE IN EXPERIMENTAL BRUCELLOSIS. B. D. CHINN, J. Infect. Dis. **64**:79 (Jan.-Feb.) 1939.

Sulfanilamide has a bactericidal and bacteriostatic effect on Brucella melitensis, Brucella abortus and Brucella suis in vitro. The drug was found to have a protective action in 100 per cent of guinea pigs inoculated with these organisms when treatment was begun immediately after inoculation.

Sulfanilamide has a definite therapeutic effect in brucella-infected guinea pigs when treatment is begun one week after inoculation. From 50 to 100 per cent of the animals (depending on the type of organisms inoculated) were uninvolved pathologically and culturally after treatment, while untreated animals were all infected with brucellas and showed characteristic lesions.

Infections in guinea pigs due to Br. abortus and Br. suis respond more satisfactorily to sulfanilamide treatment than do Br. melitensis infections.

FROM AUTHOR'S SUMMARY. TOOMEY, Cleveland.

OCCURRENCE OF "PROTOZOA-LIKE" CELLS IN THE ORGANS OF CHILDREN IN BATAVIA (CAPITAL OF JAVA AND NETHERLAND EAST INDIES). S. PRAWIROHARDJO, Nederl. tijdschr. v. geneesk. **82**:6218 (Dec. 31) 1938.

A description is given of "protozoa-like" cells found in the salivary glands and occasionally in other organs (kidneys, lungs and pancreas) in 17 of 53 necropsies on Javanese and Chinese infants under 2 years of age in Batavia. These large cells are generally regarded to be body cells changed in structure by infection with a filtrable virus. A review of the literature shows that the incidence of the condition is much higher in Java (32 per cent) than in America, where Farber and Wolbach reported its occurrence in 12 per cent of a series of children examined at the Children's Hospital in Boston.

VAN CREVELD, Amsterdam, Netherlands.

## Metabolism; Infant Feeding; Milk and Other Foods

WHOLE MILK PLUS CARBOHYDRATES IN EARLY INFANT FEEDING. E. T. WILKES, Arch. Pediat. **56**:96 (Feb.) 1939.

Forty infants from 10 days to 13 weeks of age were fed boiled whole milk with 3 to 6 per cent dextrimaltose or sucrose added. They were observed over an average period of sixteen and two-tenths weeks. Wilkes confirms the observations of others in concluding that this type of feeding may be used for the majority of infants without untoward results.

ORR, Buffalo.

DETERMINATION OF "HORMONE IODINE" IN FIVE CUBIC CENTIMETERS OF BLOOD. J. F. McCLENDON and W. FOSTER, Proc. Soc. Exper. Biol. & Med. **39**:230 (Nov.) 1938.

Five cubic centimeters of blood is added to 100 cc. of methanol (methyl alcohol); the mixture is decanted; then 100 cc. of acetone is introduced and the mixture shaken. The blood residue remains behind when the material is placed in a Visking sausage casing to evaporate. It is then analyzed by the McClendon-Bratton method (*J. Biol. Chem.* **123**:699, 1938). Potassium iodide added to the blood does not increase the iodine, while thryoglobulin iodine is entirely retained; consequently this method is provisionally considered as a method of determining "hormone iodine." In 125 determinations on human blood the "hormone iodine" was near 0.3 microgram in 5 cc., while the total blood iodine was 0.5 microgram in 5 cc. Taking 2.5 Gm. iodide by mouth did not greatly raise the "hormone iodine."

HANSEN, Minneapolis.

MINIMUM NUTRITIONAL REQUIREMENT FOR CHINA: REPORT OF THE COMMITTEE ON NUTRITION OF THE COUNCIL ON PUBLIC HEALTH OF THE CHINESE MEDICAL ASSOCIATION. Chinese M. J. **55**:301 (April) 1939.

The committee is made up of five members, coming from the departments of chemistry, biochemistry, physiology, biology and agriculture in universities and research institutions of China. The report is intended as a basis on which dietitians, health officers and social workers may formulate dietaries for actual use in present conditions. It gives in tabular form the caloric, protein, mineral and vitamin requirements for adults and for children in the home, for laborers, for preschool and for adolescent children. Studies were made which applied to the north, central and south climates for summer, winter and spring.

NEFF, Kansas City, Mo.

SUGGESTIONS FOR FEEDING REFUGEES. L. WITHAM, M. K. RUSSELL and A. V. SCOTT, Chinese M. J. **55**:324 (April) 1939.

This communication comes from the Cheeloo University, Tsinan, Shantung. It deals not only with refugees but with groups in hospitals, orphanages, school dormitories and work camps. An effort is made to improve the diet from the standpoint of a careful selection of the best foods rather than from that of cost.

Children are considered in the four age groups, and not only Chinese standards but those from the League of Nations and from America are used. Refugee diets are made up largely of grains. The limitations and objections, as well as the individual advantages of such diets are discussed, especially in regard to the requirements of vitamins and proteins for growing children and for pregnant and nursing women. Animal protein is costly in China; the protein in grain is inferior, but the country is fortunate in having soy beans, the protein of which is nearly as good as that from animals.

Several pages are devoted to the feeding of infants and older children, the available foods being listed, the quantities thereof, the calories and the protein, calcium and vitamin contents.

NEFF, Kansas City, Mo.

VALUE OF THE SWEET POTATO IN HUMAN NUTRITION. W. H. ADOLPH and H. C. LIU, Chinese M. J. **55**:337 (April) 1939.

The sweet potato is used in North China as commonly as the white potato in other parts of the world, and it has been known to be the principal item of food. Various investigators have established the amounts of vitamins contained and have found that its protein is of good nutritive value.

Adolph and Liu report the maintenance positive nitrogen balances in 3 adult subjects fed sweet potatoes alone for from five to eight weeks at a time. It is

necessary, of course, for the subject to have a sufficient intake of the sweet potato. Although health continues, fatigue occurs quickly during strenuous exercise. No mention is made of a similar study on children. NEFF, Kansas City, Mo.

CARBOHYDRATE DYSTROPHY IN AN INFANT. A. WALLGREN, Svenska läk.-tidning. **35**:2002 (Dec. 2) 1938.

A 10 month old girl who had been treated for eczema by means of a milk-free and fat-poor diet during two months showed the typical picture of the hydropic form of carbohydrate dystrophy. The child was given a protein-rich mixed diet with a rich supply of vitamins and was discharged healthy after a few weeks. The eczema, which had progressed during the period of deficient diet, was rapidly improved after the institution of the normal diet.

WALLGREN, Göteborg, Sweden.

## Vitamins; Avitaminoses

RELATION BETWEEN PLASMA ASCORBIC ACID CONCENTRATION AND DIET IN THE NEWBORN INFANT. R. L. MINDLIN, J. Pediat. **13**:309 (Sept.) 1938.

Vitamin C is usually not added to the diet of artificially fed infants until the second or third month of life. Mindlin studied the levels of vitamin C in the blood of three groups of infants at the end of the first two weeks of life. Group 1 was composed of infants receiving only breast milk; group 2, of those fed twice pasteurized cow's milk, water and karo formulas for the last four or more days. Group 3 received supplements of ascorbic acid for the duration of artificial feeding. Mindlin reports his observations as follows: The concentration of ascorbic acid in the plasma of normal 2 week old infants on breast feedings averaged 1.0 mg. per cent. That of such infants on artificial feedings for about one week averaged 0.4 mg. per cent. Lower values resulted with longer periods of artificial feedings. The addition of sufficient ascorbic acid to the diet prevented such falls in the concentration of ascorbic acid in the plasma. For optimal nutrition it seems indicated that newborn infants fed pasteurized artificial feedings should receive a daily supplement of ascorbic acid from the beginning rather than after two or three months.

RAUH, Cincinnati.

VITAMIN C CONTENT OF THE BLOOD IN NEWBORN INFANTS. A. W. FLEMING and H. N. SANFORD, J. Pediat. **13**:314 (Sept.) 1938.

The vitamin C content of the blood of 123 newborn infants was determined on the second and eighth days of life, and similar determinations were made on the blood of the mothers the same day. The blood levels of vitamin C of 51 normal adults are compared with these results. The average blood level of vitamin C was found to be for the infants 0.753 mg., for the mothers 0.884 mg. and for the adults 0.990 mg. In almost every instance the level of vitamin C in the blood of the infant was similar to that of the mother. There was no relationship between the level of vitamin C in the mother's blood and the amount of breast milk she was able to secrete. There was no correlation between the size of the baby and his blood level of vitamin C if the baby was normal. Blood levels of vitamin C were determined for 7 premature infants on different days of life and found to be considerably lower than the average. There is a slight but definite increase in vitamin C in the blood of the newborn infant throughout the first week of life with sufficeint mother's milk if the mother has an adequate intake of vitamin C. In 8 newborn infants with a diagnosis of cerebral hemorrhage the blood levels of vitamin C were found to be below the average and the mother's blood levels of vitamin C were also found to be below the average. A definite

correlation was found between the vitamin C in the mother's diet during pregnancy and the vitamin C in the blood after delivery; the higher the intake of vitamin C the higher was the level of vitamin C in the blood.

RAUH, Cincinnati.

THE BIOPHOTOMETER AS A TEST FOR VITAMIN A DEFICIENCY. C. E. SNELLING, J. Pediat. **13**:506 (Oct.) 1938.

Snelling tested a group of school children in Toronto, Canada, for dark adaptation, using a biophotometer described by Jeans and collaborators. Two tests were made within a period of three weeks, and subsequently each child was given 13,000 units of 50 per cent percomorph liver oil daily for six weeks. During this period the tests were repeated at the end of three and at the end of six weeks. After three weeks on 13,000 units of vitamin A, 8 of 17 abnormal subjects and 3 of 8 with dark adaptation on the borderline of abnormality improved; in 1 the borderline condition decreased and in 4 of 9 normal persons dark adaptation became abnormal or was on the borderline of abnormality. Similar results were obtained at the end of a six week period of vitamin A therapy. Snelling concludes that the biophotometer is unsatisfactory as a method of estimating in children the variations in dark adaptation that might be produced by vitamin A deficiency.

RAUH, Cincinnati.

EFFECT OF RIBOFLAVIN AND THIAMIN CHLORIDE UPON THE CATARACTOGENIC ACTION OF GALACTOSE. H. MITCHELL and G. M. COOK, Proc. Soc. Exper. Biol. & Med. **39**:325 (Nov.) 1938.

When rats (29 in 4 litters) were fed a ration containing 25 per cent galactose, the addition of massive doses of both riboflavin and thiamin chloride failed to protect them from the development of cataracts.

HANSEN, Minneapolis.

RACHITIC ROSARY. Y. HIRO and C. SATOMI, Acta pædiat. japon. **44**:1969 (Dec.) 1938.

The study is based on clinical data with special reference to the evidence of rickets in 229 infants under 2 years of age. The authors found the rachitic rosary in 36 per cent of the children examined and believe that it is a more reliable sign of rickets than a roentgenologic demonstration of rachitic changes in the long bones.

KATO, Chicago.

VITAMIN C CONTENT IN STARVATION. F. KOSAKI, Acta pædiat. japon. **45**:177 (Feb.) 1939.

The total vitamin C content of the normal adult rabbit varies from 0.50 to 2.11 mg. per hundred grams, the average being 1.42 mg. In the normal adult guinea pig the variations fall between 0.75 and 2.50 mg., with an average of 1.45 mg. In man the normal content ranges between 1 and 2 mg., with an average of 1.48 mg. In children under 12 years of age, the fluctuations range from 1.0 to 2.25 mg. After eighteen days of starvation the vitamin C content of the normal rabbit showed little decrease, whereas that of the normal guinea pig decreased nearly one-half in six days of starvation. In children with tuberculous meningitis and epidemic cerebrospinal meningitis, who were more or less in constant starvation, the total vitamin C content of the blood was low.

KATO, Chicago.

BIOLOGIC DEMONSTRATION OF VITAMIN C IN BREAST MILK. P. W. BRAESTRUP and H. LIECK, Hospitalstid. **81**:913 (Sept. 13) 1938.

Titrimetric investigation of the ascorbic acid content of breast milk in Copenhagen has given values varying from 1 to 10 mg. per hundred cubic centimeters.

The biologic experiments were carried out with breast milk containing 6 mg. of ascorbic acid per hundred cubic centimeters according to the dichlorophenolindophenol method of estimating it. Ten cubic centimeters daily of this milk was found sufficient to prevent scurvy in guinea pigs, which indicates an ascorbic acid content of the milk of more than 6 mg. per hundred cubic centimeters.

WALLGREN, Göteborg, Sweden.

ASCORBIC ACID SATURATION IN INFANTS. I. LAURÉN, Nord. med. tidskr. **15**:582 (April 15) 1938.

Forty-six infants from 2 weeks to 11 months of age were given 50 mg. of ascorbic acid twice a day and the urinary excretion of the substance studied. It was found that while breast-fed infants had an increased concentration of ascorbic acid in the urine even after one day (exceptionally after two days) bottle-fed infants did not show an increase earlier than the third to the twelfth day.

WALLGREN, Göteborg, Sweden.

ASCORBIC ACID DURING PREGNANCY, PARTURITION AND THE FIRST DAYS OF LIFE. A. ELMBY and P. BECKER-CHRISTENSEN, Ugesk. f. læger **100**:1047 (Sept. 15) 1938.

An examination was made of the ascorbic acid content of the serum, urine and breast milk of 200 women and of the umbilical and venous blood of their newborn babies. It was found that there is a correlation between the intake of ascorbic acid and the level of ascorbic acid in the blood and milk; the level decreases during pregnancy. The content of ascorbic acid in the serum of the newborn infant depends on the level in the mother's serum and drops during the first ten days of life. The ascorbic acid content of breast milk depends on the content in the mother's serum. If this level is subnormal it may be raised to normal by supplying 100 mg. of ascorbic acid during the first ten days of the puerperium. The level of ascorbic acid in the infant's serum depends on the amount in the mother's diet.

WALLGREN, Göteborg, Sweden.

## Hygiene; Growth and Nutrition; Public Health

FETAL AND INFANT MORTALITY. LE LORIER, Progrès méd., Oct. 22, 1938, p. 1417.

This report comes from an obstetric service and is an analysis of the fetal and neonatal mortality for the year 1936.

LESLIE, Evanston, Ill.

VALUABLE OPINION ON INFANT MORTALITY. P. O. DEZEO, Bol. Inst. internac. am. de protec. a la infancia **12**:587 (April) 1939.

Dezeo suggests the following formula as an expression of infant mortality:

$$\text{biodemographic index} = \frac{\text{birth rate} \times 1{,}000}{\text{infant death rate.}}$$

FROM EDITOR'S SUMMARY.

THE NEGLECTED MINOR AND THE NECESSITY FOR A COLOMBIAN CHILDREN'S CODE. J. A. LEÓN REY, Bol. Inst. internac. am. de protec. a la infancia **12**:601 (April) 1939.

León Rey, a judge of the juvenile court in Bogota, Colombia, speaking about the work carried out by the Association of Dormitories for Destitute Children, emphasizes, on one side, the work carried out by private organizations in his country, and, on the other, the painful state of neglected and delinquent children. He points out that this situation arises not on account of a lack of laws and regulations but on account of a lack of association of social workers which would put the legal orders into execution.

FROM EDITOR'S SUMMARY.

RESULT OBTAINED IN MEXICO BY THE RURAL SCHOOL WITH REGARD TO THE PEASANT'S LIFE. E. TORRES, Bol. Inst. internac. am. de protec. a la infancia **12**:611 (April) 1939.

Torres states that in Mexico the rural school system has been in the process of organization, little by little, since 1922, in which year the position of secretary of public education was created and the work begun under the direction of the well known writer José Vasconcelos. It is considered that 66.35 per cent of the population of the Republic is rural, that within that population there are 2,647,447 children of school age and that only a third of them have a school to go to.

FROM EDITOR'S SUMMARY.

PROCREATIONAL RESPONSIBILITY: A PROBLEM OF SOCIAL MEDICINE. A. TURENNE, Bol. Inst. internac. am. de protec. a la infancia **12**:616 (April) 1939.

Unfortunately, a sense of procreational responsibility is often absent. It should be awakened in early youth. The future of the human race requires that the race should be not more numerous but better. The resistance to measures tending to promote the diffusion of knowledge of the means of limiting procreation is the result of a tendency to prepare for future wars and is to be deplored.

FROM EDITOR'S SUMMARY.

SOCIAL REFORM AND CHILD WELFARE IN DENMARK. J. A. BAUZÁ, Bol. Inst. internac. am. de protec. a la infancia **12**:632 (April) 1939.

The social reform carried out in Denmark by Minister Steincker in 1934 places that little country among those of more advanced legislation in all that relates to problems of social welfare.

A series of laws—the law of national insurance, the law of assistance to the poor, the law of premiums to wage earners in case of accidents at work, and the law of insurance against unemployment—protects the Danish family against the consequences of illness, injury, accidents, lack of occupation and old age among the members which constitute it.

The law of assistance to the poor includes in its articles everything relating to mother and child welfare, which is placed under the direction of the National Committee for Child Welfare. It embraces the supervision of all illegitimate children below 7 years and eventually all those from 7 to 14 years of age. For this purpose an investigation of paternity is obtained either by judicial or by extra-judicial means in 90 per cent of the cases. The father is obliged to pay a pension equivalent to three fifths of the expenses for the maintenance of the child in an institution for that purpose. It is considered that the mother ought to contribute a sum equivalent to two fifths of that sum, and she should be obliged to do so if she has abandoned the home, leaving the child under the care of the father. What is interesting in the Danish law is that on petition of one of the interested parties the state may pay beforehand a part of the pension that the father has to pay, obliging him to reimburse the state for the sum whenever his funds will allow him to do so. This procedure insures that during the carrying out of the judgment the child will not be exposed to the consequences of a lack of resources affecting the mother. Although, economically speaking, the state finds this a "bad business," the compensation from the social point of view is undeniable.

FROM EDITOR'S SUMMARY.

PROTECTION OF THE CHILD AND OF THE YOUTH IN THE FAMILY AND IN THE SCHOOL. A. BERARDI, Med. inf. **10**:61 (March) 1939.

This lecture on preventive pediatrics was one of a course in Fascist culture given for school teachers.

HIGGINS, Boston.

SIGHT-SAVING SCHOOLS AND SCHOOLS FOR CHILDREN WITH VISUAL DEFECTS. M. BARTELS, Klin. Monatsbl. f. Augenh. **101**:161 (Aug.) 1938.

In a detailed and comprehensive paper, Bartels renders an account of the endeavor to further schools for the purpose of saving sight and helping children with visual deficiency. The first man to advance a request for such institutions was an Austrian, Gaheis, in 1802. The author discusses the divers phases of the subject: the prospect of visually defective children in schools for normal children, the psychologic reactions of the defective children, the definition of visual deficiency with reference to the eligibility of such children for sight-saving schools and the most efficient method of examination in helping these children. In discussing the divers forms of sight-saving schools, Bartels refers to those organized in England and in the United States. He stresses the necessity of separating the sight-saving schools entirely from schools for normal children and also from schools for the blind. Children with a high degree of myopia should not be admitted to sight-saving schools as long as they present no actual visual deficiency or are not in danger of losing their vision. The main consideration centers on the question of how the visually defective child may be best prepared for some occupation. In the chapter on the instruction at the sight-saving schools and on their equipment, Bartels refers to details pertaining to lighting, writing paper, books and size of print and also to optical aids, such as magnifying glasses and telescopic spectacles. Consideration is given to the training of the teachers and to the prospective occupation of the pupils. The recommendations of the British commission are cited in this connection.

Bartels concludes that sight-saving schools are of great importance and that institutions for the blind are far more expensive. It would be advisable, therefore, to give as good care to those afflicted with visual deficiency as is given to the blind. To quote an American author: "Every cent spent by the communities for the sight saving schools will yield a dollar." The drive for sight-saving schools must begin in the large cities. Methods to include the small cities, towns and country districts will be found later. International attention, begun at a meeting in Paris, in 1932, may be furthered and expensive experiments prevented through visits by the teachers at foreign sight-saving schools. A central international office has been established at Paris.

K. L. STOLL. [ARCH. OPHTH.]

INFLUENCE OF INFANT WELFARE ON MORBIDITY. G. CEDERGREN, Svenska läk.-tidning. **35**:1938 (Oct. 14) 1938.

About two thirds of all infants born in Göteborg, Sweden, are supervised by the infant welfare centers. In the period from 1933 to 1937 41 to 56 per thousand of the supervised children and 98 to 117 per thousand of the other children were in need of hospital treatment. The relative incidence of diseases in these two groups was as follows: infectious diseases, 32 cases to 62; intestinal disorders, 15 to 23; rickets, $<1$ to 23; tetany, 1 (during the whole five year period) to 52. The duration of hospital treatment was notably less among the supervised children and the cost of the treatment much lower.

WALLGREN, Göteborg, Sweden.

## Prematurity and Congenital Deformities

KLIPPEL-FEIL SYNDROME WITH CUTANEOUS RECKLINGHAUSEN'S DISEASE AND CONGENITAL HEMIPLEGIA: A TOMOGRAPHIC STUDY OF THE VERTEBRAL COLUMN. P. LEREBOULLET, JEAN BERNARD and R. VILLEY, Bull. Soc. pédiat. de Paris **36**:370 (June) 1938.

A girl 7 years old had a short, somewhat deformed neck due to a congenital anomaly of the cervical spine, cutaneous manifestations of Recklinghausen's disease and hemiplegia of the right side, involving the arm and leg. Both little fingers were unusually short, and the teeth showed some dystrophic changes.

BENJAMIN, Montreal, Canada.

ABSENCE OF HOMONYMOUS RIB IN TWO SISTERS; DEVIATION OF UMBILICUS IN ONE OF THEM. P. P. LÉVY, S. SERIN and P. VIVIEN, Bull. Soc. pédiat. de Paris **36**:411 (June) 1938.

The twelfth rib was absent in each of two sisters. In one the umbilicus was situated to the right of the midline without any visible cicatrix to explain the displacement.

BENJAMIN, Montreal, Canada.

CAUSES OF PREMATURE BIRTH. T. BRANDER, Finska läk.-sällsk. handl. **81**:1010 (Oct.) 1938.

A study was made of 376 premature children of school age with regard to the cause of their prematurity. The principal obstetric causes were twin births, toxicosis of pregnancy and acute infectious diseases. About 50 per cent of the cases were etiologically obscure—to judge from the records of the maternity hospital. Fifteen per cent of the mothers had suffered from goiter or signs of thyrotoxicosis, which the author regards as an etiologic factor. In a few cases, too, the anthropometric measures of the mother were small. There was no demonstrable hereditary predisposition to premature birth.

WALLGREN, Göteborg, Sweden.

ANAMNESTIC AND CATAMNESTIC REPORTS OF THE DEVELOPMENT OF THREE HUNDRED AND SEVENTY-SIX PREMATURE CHILDREN AND THEIR SUBSEQUENT FATE UP TO THE END OF THEIR SCHOOL AGE. T. BRANDER, Finska läk.-sällsk. handl. **81**:1183 (Dec.) 1938.

The incidence of a series of developmental anomalies and diseases was studied in two groups of premature children of school age: (1) those whose birth weight was below 2,000 Gm. and (2) those whose birth weight was above 2,000 Gm. The lower the birth weight, the more retarded was the development of the teeth, of the faculty to sit, stand and walk, and of speech. Puberty was often retarded; on the other hand, sometimes it was precocious. A more or less pronounced physical underdevelopment at school age was rather common. Nine per cent of the children were mentally deficient. Among the children who attended ordinary schools the stupid pupils were twice as numerous as the clever ones. Convulsions occurred twice as frequently in the lower weight group.

WALLGREN, Göteborg, Sweden.

OPERATIVE TREATMENT OF CLEFT PALATE FROM A SOCIAL AND MEDICAL POINT OF VIEW. E. PERMAN, Svenska läk.-tidning. **35**:2025 (Dec. 9) 1938.

It is important that the operation for closure of a cleft palate should be performed when the child is 2 years old. The parents should be informed about the necessity to consult a surgeon at that time. In Sweden the state pays for the expenses of the parents in connection with the treatment of cleft palate, and the work is confined to a few hospitals with surgeons especially trained in the technic of such operations. During the last two years Perman has operated (method of Ernst-Axhausen) on 60 children with cleft palate, of whom 32 were older than 3 years. The result was satisfactory in 54. One child died. In the remaining 5 the aperture could not be closed.

WALLGREN, Göteborg, Sweden.

ACRANIA DIAGNOSED BEFORE PARTURITION. O. HOLM, Svenska läk.-tidning. **35**: 2165 (Dec. 30) 1938.

Holm reports a case of acrania in a fetus in a 30 year old pregnant woman. The condition was diagnosed roentgenologically.

WALLGREN, Göteborg, Sweden.

CARE AND TREATMENT OF CHILDREN WITH CLEFT PALATE AND HARELIP. E. EDBERG, Svenska läk.-tidning. **35**:2171 (Dec. 30) 1938.

Congenital malformation of the lips and the palate is a recessive hereditary disease. Direct inheritance was demonstrated in 15 per cent of cases. Several siblings may suffer from the disease in different variations if the heredity is present on both the paternal and the maternal side. Sterilization has hitherto never been performed. Boys are more predisposed than girls; of 489 patients, 58 per cent were boys. In 67 per cent the malformation was localized on the left side. More than 50 per cent of the patients suffered from total deformity. It is considered that there is 1 case of this malformation in every 1,000 births. Six of the patients were twins. There are often other types of malformation present. Imbecility is rare, but many children with cleft palate (26 per cent) are admitted to classes for dumb children because of a disorder of speech and deafness. Operation on the lips is recommended from the third month on. The palate ought to be operated on at 2 to 3 years of age. Many patients need prosthetic treatment after operation, and cooperation with the dentist and the orthodontist is necessary. The treatment of the malformation should be confined to a few centers where a trained surgeon specializes in this disease and where cooperation with the dentist and the orthodontist can be assured.

WALLGREN, Göteborg, Sweden.

ETIOLOGY OF TOWER SKULL. A. J. DE LEEUW-AALBERS, Maandschr. v. kindergeneesk. **8**:89 (Nov.) 1938.

This is a discussion of the different theories as to the etiology of turricephaly and a description of the anomaly as observed in an 8 year old girl with a primary cerebral lesion. The latter must be regarded as the cause of the deviation in the form of the skull.

VAN CREVELD, Amsterdam, Netherlands.

## Newborn

A CASE OF SEVERE ANEMIA OF THE NEWBORN WITH ERYTHROBLASTEMIA; CURE. M. LELONG and M. LACOMME, Bull. Soc. pédiat. de Paris **36**:422 (June) 1938.

An infant showed severe anemia when 5 days old. Maternal blood was given in 5 cc. amounts intramuscularly and liver extract by mouth. Later iron and manganese were added. No icterus, edema or hemorrhage was noted. The liver, spleen and lymph nodes were not enlarged. The general condition was good. At 18 months the hemogram and the smear of bone marrow obtained by sternal puncture were normal.

BENJAMIN, Montreal, Canada.

EPIPHRENIC DIVERTICULA OF THE ESOPHAGUS IN A NEWBORN CHILD. M. LELONG, P. AIMÉ and J. BERNARD, Bull. Soc. pédiat. de Paris **36**:431 (June) 1938.

A newborn boy had vomited since birth and was losing weight. Two small dark blood clots were present in the vomitus on the third day, then streaks of dark blood in the stool. Roentgen examination revealed dilatation of the esophagus just above the diaphragm to the left and to the right.

BENJAMIN, Montreal, Canada.

CHRONIC MENINGITIS IN A NEWBORN INFANT WITH ENCEPHALOCELE. S. HINDSE-NIELSEN, Hospitalstid. **81**:220 (March 1) 1938.

A newborn boy had an occipital encephalocele the size of a hen's egg. He died on the sixth day of life, five days after extirpation of the cystic tumor. The histologic examination of the encephalocele showed signs of chronic meningitis. The

mother was healthy and had not suffered from any infectious disease during pregnancy. The possibility that the meningitis was an expression of a reaction to traumatic lesions (there were signs of small hemorrhages) or was due to intrauterine infection is discussed.

WALLGREN, Göteborg, Sweden.

FAMILIAL OCCURRENCE OF OBSTETRIC CEREBRAL LESIONS. M. LINDSTEN, Nord. med. tidskr. **15**:583 (April 15) 1938.

Two newborn siblings suffered from symptoms of a cerebral lesion (cyanosis; convulsions; sanguinolent xanthomatotic liquor). In the first case parturition was spontaneous; in the second force was used. The mother and 3 of her sisters and brothers had suffered during infancy, from birth on, from convulsions, and the mother's father had displayed the same symptoms during his first month of life.

WALLGREN, Göteborg, Sweden.

HEMORRHAGIC DIATHESIS IN NEWBORN BABIES. A. WALLGREN, Svenska läk.-tidning. **35**:1999 (Dec. 2) 1938.

1. A full term girl, delivered spontaneously, showed rapidly increasing cephalhematoma and cutaneous ecchymoses. She was examined on the third day. The thrombocyte count was 175,000, and the retraction of the blood clot was normal. The bleeding time was one hour. The minimum value of hemoglobin was 30 per cent. The erythrocyte count was 1,000,000. The bleeding continued until the sixth day. The bleeding time then was normal. The child was discharged healthy, with normal blood findings, without iron treatment (endogenous iron from the hematoma). The infant was treated with repeated intramuscular injections of blood.

2. A full term boy, delivered normally, had convulsions, bleeding from the gums, and ecchymoses and purpuric spots in the skin shortly after birth. He was examined on the second day. There were slight anemia and leukocytosis. The thrombocyte count and the retraction of the blood clot were normal. The clotting time was eight minutes; the bleeding time, several hours. He died from intracranial hemorrhage on the fifth day.

3. A full term boy, normally delivered, had purpuric spots in the skin, bleeding from the umbilicus and melena on the second day. Next day moderate anemia was noted. The thrombocyte count and the retraction of the blood clot were normal. The bleeding time was eight hours; the clotting time, eighteen minutes. Injections of blood had no effect on the bleeding. The hemoglobin content was 54 per cent. A fatal outcome appeared on the fifth day. Postmortem examination disclosed extensive hemorrhages of the internal organs.

There are known to be conditions intermediate between ordinary melena and that described here. Wallgren is of the opinion that these various kinds of hemorrhagic diathesis of newborn babies are of the same genesis.

WALLGREN, Göteborg, Sweden.

RELATION OF BIRTH WEIGHT TO NEONATAL MORTALITY RATE. H. BJERNE, Ugesk. f. læger **100**:368 (April 7) 1938.

The neonatal mortality rate of 9,689 children was studied. The infants were classed in different groups according to their birth weights: less than 1,000 Gm.; 1,000-1,499 Gm.; 1,500-1,999 Gm.; 2,000-2,499 Gm. All children weighing less than 1,000 Gm. at birth died. In the other three groups the mortality rates were 81.9, 34.4 and 13.8 per cent, respectively. The lowest mortality rate was that of a group weighing from 3,000 to 3,999 Gm. From 4,500 Gm. on, the mortality rate again increased rapidly and reached its maximum value of 33 per cent with birth weights above 5,000 Gm.

WALLGREN, Göteborg, Sweden.

## Acute Contagious Diseases

ENDEMIC TYPHUS FEVER IN TEXAS. H. KEMP, Am. J. Trop. Med. **19**:109 (March) 1939.

Endemic typhus fever in Texas shows but few differences from the same form of disease in the other Southern states. It usually lasts fourteen days, is free from complications and carries a low mortality. It tends to spare infants, children and aged persons. The greatest incidence is in males of the working class, particularly those working in grocery stores, grain depots and warehouses.

It appears to be almost identical with tropical (Malayan) typhus except for a difference in vectors and a failure of serum from the patients in Texas to agglutinate the anindologenic strain of Proteus. It also differs from Brill's disease clinically and epidemiologically.

BUSPEE, Augusta, Ga.

THE BLOOD STREAM IN EXPERIMENTAL POLIOMYELITIS. F. B. GORDON and E. H. LENNETTE, J. Infect. Dis. **64**:97 (March-April) 1939.

Gordon and Lennette attempted to transfer virus from monkeys which had been inoculated with the virus of poliomyelitis by repeatedly transfusing the blood of these monkeys to susceptible animals while at the same time damaging the blood–central nervous system barrier of the recipient monkeys. They were not able to demonstrate virus in 14 samples of blood, ranging in volume from 10 to 45 cc., from paralyzed monkeys nor in 28 samples of blood, ranging from 8 to 30 cc., taken from infected monkeys before paralysis appeared. Repeated intranasal inoculation of 7 monkeys with the virus after their olfactory bulbs had been destroyed did not result in poliomyelitis, in the appearance of virus in the blood or in a detectable immunologic response. Thus, no indication was found that virus is adsorbed by way of the blood stream or by other routes from nasal or alimentary mucosa. The results show that the virus of poliomyelitis either does not enter the blood stream intranasally or, if it does, enters in amounts too small to be detected by the methods applied.

TOOMEY, Cleveland.

EXPERIMENTAL INFECTION IN THE MOUSE PRODUCED BY INTRATRACHEAL INOCULATION WITH AN ATYPICAL PERTUSSIS ORGANISM. W. L. BRADFORD and M. WOLD, J. Infect. Dis. **64**:119 (March-April) 1939.

With intratracheal or intranasal inoculation of a recently described pertussis-like organism a definite pulmonary lesion is produced in mice. This lesion is of the order of interstitial pneumonia and resembles essentially that produced by inoculation with Haemophilus pertussis.

TOOMEY, Cleveland.

MUMPS MENINGO-ENCEPHALITIS. T. L. BIRNBERG, Minnesota Med. **22**:173 (March) 1939.

Birnberg reports 38 cases of mumps meningoencephalitis observed during the past five and one-half years. He feels that increasing awareness of this complication will result in more frequent recognition of it and will indicate it to be the most common complication of preadolescent mumps. The symptoms generally appear from one to ten days after the onset and are headache, vomiting, fever, moderate rigidity of the neck and Kernig's sign. Spinal fluid obtained by lumbar puncture shows absence of a Nonne-Apeit reaction and lymphatic pleocytosis (usually 100 to 300 cells). He feels that the relatively mild symptoms and the rather high cell count are valuable diagnostic criteria. The treatment, he feels, should be symptomatic, and he states that the prognosis is good.

ANDERSON, Minneapolis.

VITAMIN C NUTRITION AND SUSCEPTIBILITY TO DIPHTHERIA AS POSSIBLE FACTORS IN EPIDEMIOLOGY OF POLIOMYELITIS. W. G. HEASLIP, Australian J. Exper. Biol. & M. Sc. **16**:287 (Dec.) 1938.

Heaslip states that toward the end of 1937 an epidemic of poliomyelitis began in South Australia. A number of the earlier cases occurred in an area of a city in which immunization against diphtheria had been carried out previous to the epidemic, and Dwyer observed that the majority of the cases of poliomyelitis were those of children who were not immunized to diphtheria. Immunization had been carried out without previous Schick tests. In 1937 Jungeblut reported that vitamin C had a therapeutic effect when injected subcutaneously into monkeys inoculated with the virus of poliomyelitis. A review of the literature on susceptibility to diphtheria and to poliomyelitis showed in each case a correlation with the results of certain experimental work with vitamin C. In 1917 Zingher reported that a positive reaction to the Schick test was given in a disproportionately large percentage of cases of poliomyelitis. Comparing the patients with poliomyelitis who were not immunized to diphtheria with the controls, Heaslip finds that the age group of 12 years and over gave substantially the same percentage of positive Schick reactions as the control group. This is possibly the most extraordinary result obtained, as this age group contained 42 per cent of the patients and their ages ranged up to 60 years; 30 per cent of them were 21 years of age or more. Admitting that some of these were rural dwellers, the figure is still high in a state in which diphtheria is moderately prevalent. The same may be said of the whole group, especially when it is considered that fewer than a third of the patients were less than 6 years of age. Of the 238 patients tested, 21 had been artificially immunized, and 9 had had diphtheria. Eight of these 30 gave a positive reaction to the Schick test. In a control group of 359 persons, of whom 4 had had diphtheria and 355 had been artificially immunized, only 2 gave a positive Schick reaction. One of these had received only 0.5 cc. of anatoxin and the other only 1 cc. The author is tempted to suggest that the result in these 2 cases is due to the fact that those who still gave a positive Schick reaction after immunization contracted poliomyelitis. These figures support the idea of a constitutional defect underlying susceptibility to the two diseases, and it is not surprising to learn that several of the patients with poliomyelitis have, within a few months, contracted diphtheria despite immunization. Dwyer reported that few of these immunized patients contracted poliomyelitis. This contrasts sharply with the report of Henry and Johnson that 51 per cent of their patients with poliomyelitis had previously been immunized. The explanation is probably that Dwyer's group was immunized without previous Schick tests; that is, many of them did not require them, whereas it is justifiable to assume that all of the latter group gave positive Schick reactions prior to immunization. From these results, supported as they are by Zingher's observations on a much larger group, it is evident to Heaslip that there is a greater susceptibility to poliomyelitis in persons giving a positive Schick reaction than in those who give a negative reaction. Conversely, there is a larger percentage susceptible to diphtheria among those who contract poliomyelitis than in the normal population. The urinary excretion of vitamin C for various groups of infected and noninfected persons was estimated, and the conclusion is drawn that, while the usual sequence of events is a decreased excretion of vitamin C after infection, it is probable that a low level of vitamin C nutrition predisposes to infection and severity of attack. It is probable that there is a relation between nutrition and the age incidence in this disease.

J. A. M. A.

CASE OF CUTANEOUS AND CONJUNCTIVAL DIPHTHERIA. R. M. BATES, Brit. J. Dermat. **51**:76 (Feb.) 1939.

Bates reports a case in which the clinical picture at first suggested varicella. The formation of membranes on the conjunctivas finally led to a diagnosis of diphtheria. A cure was obtained with the administration of antitoxin.

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

REACTIONS BETWEEN DIPHTHERIA TOXIN AND ANTITOXIN. C. G. POPE and M. HEALEY, Brit. J. Exper. Path. **19**:396, 1938.

A photoelectric method has been used to study various phases of the Ramon flocculation reaction between diphtheria toxin (or toxoid) and antitoxin. The following observations were made: The production of opacity is more rapid in a mixture containing a dose of antitoxin equivalent to that of toxin than in one in which the dose of antitoxin is either more or less than that of toxin. The rate is affected more by a decrease than by an increase in the amount of antitoxin, probably because mixtures containing two equivalents eventually develop a greater opacity than the mixture containing one equivalent. The rate is increased if the antitoxin is added in two fractions. A preformed equivalent mixture gave high reactivity with more antitoxin, and under certain conditions a second stage may be observed, which is the resolution of preformed aggregates by an excess of antitoxin. Mixtures of toxin and antitoxin in varying proportions at equilibrium gave opacity curves similar in shape to the curves for the nitrogen content of floccules of varying composition, the maxima occurring at approximately the same place. This method of investigation is being used in further studies of precipitin reactions.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

DIPHTHERIA AND ITS PROPHYLAXIS. J. J. LEUNDA, Bol. Inst. internac. am. de protec. a la infancia **12**:656 (April) 1939.

Leunda began his lecture by expressing his pleasure in addressing the professors who made up his audience, for, he said, the teacher ought to be an effective collaborator in all social work. He pointed out the extension and gravity of diphtheria in Uruguay. After discussing diphtheria, he gave rules for the prophylaxis of the disease.

FROM EDITOR'S SUMMARY.

EXPERIMENTAL TRANSMISSION OF POLIOMYELITIS TO CATTLE. E. FRAUCHIGER and W. HOFMANN, Schweiz. med. Wchnschr. **68**:1140 (Oct. 8) 1938.

Frauchiger and Hofmann cite Frauchiger's report (A Case of Spontaneous Poliomyelitis in an Animal, ibid. **111**:74 [July 2] 1938). His observations induced them to attempt the transmission of poliomyelitis to cattle. Poliomyelitis material (brain and spinal cord) from human subjects was inoculated into 3 heifers aged between 12 and 18 months. Large doses were given, and the material was introduced by three different routes (intranasal, intraperitoneal and intraspinal). Only 1 of the animals was not subjected to intraspinal administration. Except for increases in temperature at the onset, general symptoms, such as gastrointestinal disturbances, nasal discharge and sweating, were absent. Moreover, there were no signs of meningeal irritation. However, after two or three days signs of paralysis appeared in the extremities, particularly the posterior. The paralytic symptoms increased until the seventh day. One animal showed their persistence in about the same intensity, whereas in another they diminished but never disappeared. During the severest stage of the disease the animals had an ataxic walk and frequently fell. Complete flaccid paralysis was not observed. The third animal, which had not been subjected to intraspinal inoculation, showed mild paresis, which soon disappeared. In the fourth week after the inoculation, bilateral atrophy of the gluteal musculature was observed in 1 animal. In 1 animal atrophy was observed in the musculature of the pelvis and thighs, as well as in the right foreleg. The cerebrospinal fluid of the animals revealed changes indicative of organic disease of the central nervous system, but since microscopic studies have not yet been made the authors are unable to state whether the disease process is identical with that of poliomyelitis. However, further investigations will be devoted to such microscopic studies and to attempts to transmit the disease further by means of material obtained from these animals.

J. A. M. A.

IMMUNITY TO SCARLET FEVER IN DIFFERENT DISTRICTS OF FINLAND. J. WICKSTRÖM, Finska läk.-sällsk. handl. **81**:15 (Jan.) 1938.

The Dick test was carried out on 21,000 Finnish soldiers from different parts of the country. It was found that the test was positive much more frequently among those from the southwestern part of Finland, where scarlet fever is most prevalent, than among those from other parts of the country, with a lower incidence of the disease. Wickström suggests that this somewhat surprising result depends on constitutional immunobiologic differences of the population in these two parts of Finland.

WALLGREN, Göteborg, Sweden.

SEASONAL VARIATIONS IN OCCURRENCE OF AND SUSCEPTIBILITY TO SCARLET FEVER. J. WICKSTRÖM, Finska läk.-sällsk. handl. **81**:21 (Jan.) 1938.

Scarlet fever is most prevalent from January to April, inclusive, while immunity to the disease, as shown by the Dick test, is lowest from April to June.

WALLGREN, Göteborg, Sweden.

EXPERIMENTAL VACCINATION AGAINST SCARLET FEVER. J. WICKSTRÖM, Finska läk.-sällsk. handl. **81**:27 (Jan.) 1938.

The incidence of morbidity in the vaccinated group (1,625 persons vaccinated with streptococcus toxin) was 4 per cent; in the control group (1,240 persons) it was 15.8 per cent.

WALLGREN, Göteborg, Sweden.

ACUTE POLIOMYELITIS IN TWINS. C. A. BERGSTRÖM, Finska läk.-sällsk. handl. **81**:33 (Jan.) 1938.

This is a study of 4 pairs of uniovular twins, 7 pairs of biovular twins of the same sex and 6 pairs of biovular twins of different sexes in each of which at least 1 twin had had poliomyelitis. In only 1 of the 4 pairs of uniovular twins did poliomyelitis occur in both children, but these 2 children showed different types and severity of the disease, and 1 of them died. In the 16 remaining pairs of twins only 1 child in each pair fell ill with the paralytic type of the disease. In 6 of the children not paralyzed there occurred at the same time as the poliomyelitis in the twin symptoms and signs that perhaps may be interpreted as caused by the nonparalytic type of the disease. In 16 pairs the twins lived together and may have been exposed to the same contagion; in the seventeenth pair the children lived separately. It has not been possible to show why only 1 twin in each of these 16 exposed pairs fell ill. Bergström concludes that this study does not speak in favor of a specific disposition toward poliomyelitis in certain families.

WALLGREN, Göteborg, Sweden.

THE BLOOD PICTURE AFTER INTRACUTANEOUS VACCINATION AGAINST SMALLPOX. B. KNAPE, Finska läk.-sällsk. handl. **81**:579 (June) 1938.

No significant difference was found in the blood picture after intracutaneous vaccination (12 children) as compared with that after percutaneous vaccination (6 children).

WALLGREN, Göteborg, Sweden.

ENCEPHALITIS AFTER GERMAN MEASLES. C. GRILL, Nord. med. tidskr. **15**:400 (March 5) 1938.

Grill reports on encephalitis following rubella as observed in 2 girls 12 and 16 years of age. They fell ill on the sixth and eighth days, respectively, after the eruption, with symptoms of an involvement of the central nervous system and with an increased cell content of the spinal fluid. Complete recovery occurred in a few weeks.

WALLGREN, Göteborg, Sweden.

RESPIRATOR TREATMENT OF POLIOMYELITIS. N. FAXÉN, Svenska läk.-tidning. **35**: 1856 (Nov. 11) 1938.

Faxén reports on 15 patients with poliomyelitic respiratory failure who were treated in a respirator. Two of the patients survived. One of them, a boy of 13, had to remain in the respirator for four weeks. At discharge he was able to walk, but his arms were paralytic; the right one was totally paralyzed. He now attends school regularly and is able to write with his left hand. A second patient, a woman aged 22, is now sufficiently strong to attend to her usual household duties. Faxén emphasizes the important role the respirator plays in lessening the sufferings and the symptoms of suffocation in patients with poliomyelitis, even if life cannot be saved.

WALLGREN, Göteborg, Sweden.

STATISTICS OF THE CAUSES OF DEATH AND POSTVACCINAL ENCEPHALITIS. H. PEETERS and M. G. NEURDENBURG, Nederl. tijdschr. v. geneesk. **82**:5851 (Dec. 10) 1938.

Peeters and Neurdenburg defend their opinion that the statistical calculations of Julius by which he tries to prove that encephalitis occurring in infants after vaccination is a coincidence do not prove anything either against or in favor of a causal relation between vaccination and postvaccinal encephalitis at whatever age. They say that by the statistical method no solution of this intricate problem can be found. In the statistics of causes of death no evidence is found which confirms the common practical experience in this country and abroad that in spite of the greater liability of young infants to cerebral irritation they are less liable to postvaccinal encephalitis than older children. The great number of unknown factors make any statistical calculation impossible.

VAN CREVELD, Amsterdam, Netherlands.

CONVALESCENT SERUM IN TREATMENT OF MEASLES. W. A. TIMMERMAN, Nederl. tijdschr. v. geneesk. **83**:1346 (March 25) 1939.

Measles convalescent serum was used for 98 Dutch children in homes and in various institutions (a children's hospital, a sanatorium and others). In 23 cases partial protection was aimed at, and attained in 22 cases; in 1 case protection was complete. In 75 cases complete protection was the purpose, and the effect was successful in 50; in 20 cases a very slight morbilloid condition resulted; in 5 no influence of the serum on the course of the disease was seen. The cases in which the result did not quite come up to expectations are discussed in detail. The dosage, the day of injection and the indications for the treatment are outlined. Consideration is given to substitution of adult serum or placental extract for convalescent serum. Provisionally, convalescent serum must be preferred.

VAN CREVELD, Amsterdam, Netherlands.

## Acute Infectious Diseases

SERUM THERAPY FOR INFECTIONS WITH STREPTOCOCCI. A. E. SHEPLAR, M. J. SPENCE and W. J. MACNEAL, Arch. Surg. **37**:772 (Nov.) 1938.

This report deals with the treatment of 66 patients for hemolytic streptococcus infections by the use of the concentrated antistreptococcus serum of the New York State Department of Health. In this group 18 died and 48 recovered—a death rate of 27.3 per cent. The case records are all presented and the method of administration of the serum is discussed. Among the patients with severe infection recoveries were noted with the use of three different preparations of streptococcus serum, given either alone or in combination with multiple transfusions, with bacteriophage and with sulfanilamide.

KAISER, Rochester, N. Y.

EFFECTS OF SULFANILAMIDE ON BRUCELLA MELITENSIS, VAR. MELITENSIS, ABORTUS, AND SUIS. E. E. MENEFEE JR. and M. A. POSTON, J. Bact. **37**:269 (March) 1939.

Menefee and Poston attempted to determine the effect of sulfanilamide on cultures of Brucella in vitro and on experimental infections in a susceptible species of animals. The problem was divided into four parts: (1) the in vitro action of sulfanilamide on cultures of Brucella; (2) the in vitro action of related compounds; (3) the in vitro action of sulfanilamide and antibrucella serum, and (4) the action of sulfanilamide on experimental brucellosis in the guinea pig.

Their findings in guinea pigs support the clinical observations in suggesting that the bacteriostatic action allows the normal defense mechanisms of the body to cope adequately with the invading bacteria. STOESSER, Minneapolis.

ANTIRABIC IMMUNIZATION. I. J. KLIGLER and H. BERNKOPF, Brit. J. Exper. Path. **19**:378, 1938.

Experiments are reported which indicate that formaldehydized tissue cultures of rabies virus possess considerable immunizing capacity for mice if injected intraperitoneally. The immunity to an intracerebral infection is incomplete; a little less than half of the mice given five to seven injections of the vaccine possessed solid immunity to 10 lethal intracerebral mouse doses; about 42 per cent possessed no immunity. Immunity to an intraperitoneal or a subcutaneous infection is more easily established. Even a single intraperitoneal treatment with the inactivated culture virus is sufficient to protect mice against an intraperitoneal infection with a dose of fresh virus which kills about two thirds of the control mice. A similar immunity is conferred against a subcutaneous infection except that a larger amount of vaccine is required. Of special interest, perhaps, are the data showing that immunized mice which survive an intraperitoneal infection possess a greater degree of immunity than do untreated mice which survive such an infection. Primary treatment with inactive virus affects to a marked extent the immunity of these mice to an intracerebral infection. Mice which received diluted vaccine (1:10) or fewer doses possessed a lower degree of immunity than the others, although all of them survived an intraperitoneal or a subcutaneous infection with fresh brain virus. Only half of the mice which survived an intraperitoneal infection without previous vaccination were immune to an intracerebral infection, whereas 84 per cent of previously immunized mice proved immune. A single dose of a rabies virus culture which had a very low virulence for mice, if injected intraperitoneally, conferred on the treated mice a high degree of immunity against a subsequent intracerebral infection with test brain virus.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

AGGLUTINATION OF SUSPENSIONS OF VIRUS-LIKE PARTICLES PREPARED FROM EXUDATES IN ACUTE RHEUMATIC FEVER. G. HARDY EAGLES and W. H. BRADLEY, Quart. J. Med. **8**:173 (April) 1939.

Eagles and Bradley have demonstrated agglutination of suspensions of rheumatic elementary bodies by the serums of 54 patients who had pains in their joints due to rheumatic fever, arthritis or arthropathies of unclassified types. No relationship existed between the agglutinin titer and the clinical picture. There was no evidence that the titer paralleled the antistreptolysin titer or the sedimentation rate.

BRADFORD, Rochester, N. Y.

UNDULANT FEVER IN A CHILD. H. HELLSTEN, Nord. med. tidskr. **15**:584 (April 15) 1938.

A boy of 4½ years fell ill with symptoms of stomatitis and fever. Examination showed splenomegaly and leukopenia; the serum test for Bang's disease was

positive. The fever curve had the typical undulant character, with five different waves during the three months' duration of the illness. The patient recovered.

WALLGREN, Göteborg, Sweden.

RHEUMATIC SYMPTOMS IN PATIENTS WITH ERYTHEMA NODOSUM. N. SKIÖLD, Nord. med. tidskr. **15**:595 (April 15) 1938.

Of 128 adults with erythema nodosum, 27, or 21 per cent, showed symptoms and signs of arthritis. Most of them had very high sedimentation rates. In some cases the sedimentation rate was increased for a long period without any demonstrable changes in the lungs. This was supposed to be due to concomitant rheumatic involvement of the heart. Such involvement was demonstrated in 2 patients.

WALLGREN, Göteborg, Sweden.

A DOG AS THE SOURCE OF INFECTION IN PARATYPHOID FEVER. K. E. MAGNUSSON, Svenska läk.-tidning. **35**:1307 (Aug. 19) 1938.

Paratyphoid disease in a pregnant dog (Salmonella abortus canis) was transmitted to 4 human beings. In the latter the infection produced rather severe disease, with high fever and prostration. The patients recovered.

WALLGREN, Göteborg, Sweden.

JUVENILE RHEUMATISM. S. SIWE, Svenska läk.-tidning. **35**:1379 (Aug. 26) 1938.

Siwe emphasizes that rheumatic fever is a disease which is most common in childhood, with the highest frequency at 8 to 12 years of age. The symptoms are not infrequently atypical, and the diagnosis is often more difficult in children than in adults; the disease therefore is more often overlooked. Of 152 children with the disease, 124 displayed clinical signs of endocarditis, 87 of myocardial damage and 21 of pericarditis. The annular erythema was demonstrable in 10 per cent and nodules in 5 per cent of all patients. The most important treatment is rest in bed for a sufficiently long period, which may last for many months and therefore is difficult to arrange in the child's home. A sufficient number of hospital beds is necessary, and there should be accommodations for convalescent care of discharged children.

WALLGREN, Göteborg, Sweden.

SEDIMENTATION TESTS IN SOME COMMON INFECTIONS IN CHILDREN. N. BLUME, Svenska läk.-tidning. **35**:1471 (Sept. 16) 1938.

Only 30 per cent of children with pseudocroup (59) showed an evident but usually moderate increase of the sedimentation rate. Of those with acute pneumonia (315), less than 1 per cent had a low rate; most of them, a very high one. Of those with acute pharyngitis (329), a distinct and often high sedimentation rate was demonstrated for 52 per cent. Of those with acute bronchitis (247), 16 per cent had a normal or almost normal sedimentation rate.

WALLGREN, Göteborg, Sweden.

AN EPIDEMIC OF PARATYPHOID FEVER IN A MATERNITY HOSPITAL. N. FAXÉN, Svenska läk.-tidning. **35**:1959 (Nov. 25) 1938.

An epidemic of paratyphoid fever occurred in the maternity hospital of Göteborg. In all, 23 adults and 15 newborn babies were affected. The source of infection was a bacilli-carrying mother. The contamination occurred probably through contact. Some of the infants may have been infected by way of breast milk. In 50 per cent of the adults the infection produced clinical symptoms of paratyphoid fever; the other women remained healthy, although they excreted

bacilli in their stools. Only 1 of the infants fell ill. It died from paratyphoid-meningitis. The other 14 babies remained healthy, but 1 of them excreted bacilli in the stools for seven months.

WALLGREN, Göteborg, Sweden.

A CASE OF ECHINOCOCCUS CYST OF THE LUNGS. A. DEKKER-JONKER, Maandschr. v. kindergeneesk. **8**:231 (March) 1939.

Dekker-Jonker describes the clinical picture of an echinococcus cyst in a child of 6 years, who probably became infected from a dog living in the same house. As the characteristic roentgen picture and eosinophilia were not found, the diagnosis was made only after an exploratory puncture which caused rupture of the cyst into a bronchus. This was followed by anaphylactic shock. One year after that an abscess was found at the same place. The author mentions the different risks of a puncture in cases in which echinococcus cyst has been diagnosed with certainty.

VAN CREVELD, Amsterdam, Netherlands.

## Chronic Infectious Diseases

TREATMENT OF TUBERCULOSIS OF THE SPINE BY SPINAL FUSION: RESULTS IN THREE HUNDRED AND NINE CHILDREN LESS THAN TEN YEARS OF AGE. W. E. SWIFT, J. Pediat. **13**:248 (Aug.) 1938.

Swift as spokesman for the staff of the New York Orthopaedic Dispensary and Hospital states that it is their unanimous opinion that fusion operation is the treatment of choice for children and adults who have tuberculosis of the spine. Rest and removal of trauma are accepted as essential for the healing of a tuberculous focus. When the conservative treatment is used, every act of respiration moves the vertebral joints to a certain extent; contraction of the abdominal and spinal muscles transmits stress and motion to the area of vertebral disease, and where there is loss of bone substance due to the disease all of these motions and stresses become exaggerated. If the posterior intervertebral joints and laminas are fused, the motions due to respiratory and muscular contractions will be eliminated over the area fused. Spinal fusion also supplies a strong bony support over the involved vertebrae and tends to lessen, if not entirely to prevent, the forward collapse of the bodies which have been more or less destroyed.

Three hundred and nine children less than 10 years of age have been treated by spinal fusion. Good results were obtained in 74 per cent. By a good result Swift means that the child is well, leading an active normal life and is without danger of return of the disease at the original site. There are no symptoms or physical signs referable to the spine other than the deformity and limitation of motion which may be present. The roentgenograms show a completely subsided lesion with a tendency toward healthier texture in the soft tissue and bone whether or not there is complete bony union of the vertebral bodies. Approximately 45 per cent of the children with good results have followed an optimum course after fusion and have completed their hospitalization and need for support in ten months. Swift believes that when tuberculosis of the spine is recognized and attacked earlier, more and more children will be found in the latter group.

RAUH, Cincinnati.

VITAMIN C IN TUBERCULOSIS: THE EFFECT OF SUPPLEMENTARY SYNTHETIC VITAMIN C ON THE URINARY OUTPUT OF THIS VITAMIN BY TUBERCULOUS CHILDREN. T. S. BUMBALO and W. W. JETTER, J. Pediat. **13**:334 (Sept.) 1938.

A group of tuberculous and normal children, both on approximately the same basic amount of dietary vitamin C, i. e., 55 to 65 mg. daily, were compared as to the urinary excretion of vitamin C, after which 50 mg. of synthetic vitamin C was added to the daily diet of each child. The normal group showed an immediate

rise in the amount of vitamin C excreted, whereas the tuberculous group, in which the average basic excretion was 6.4 mg. per twenty-four hours, required an average of 750 mg. in fifteen days to produce a rise in excretion to 10 mg. per twenty-four hours. The maximal output (23 mg. per twenty-four hours) was obtained on the twenty-fourth day after 1,200 mg. had been ingested. Subsequent feeding produced no further increase. On discontinuance of the adding of vitamin, the excretion of the tuberculous group promptly fell to the previous subnormal levels. This study points to hypovitaminosis C in active tuberculosis and suggests increased intake of vitamin C as a therapeutic measure. RAUH, Cincinnati.

EVALUATION OF SEROLOGIC TESTS FOR CONGENITAL SYPHILIS WITH SPECIAL REFERENCE TO THE NEONATAL PERIOD. J. A. V. DAVIES, J. Pediat. **13**:341 (Sept.) 1938.

Fifty-six infants born of syphilitic mothers were studied by physical examinations and repeated Davies-Hinton microflocculation tests of serum obtained by cutaneous puncture, by study of roentgen films of the long bones and by supplementary tests of blood obtained by venipuncture. An estimate of the strength of the reaction in the infant and of that in the mother was made. Twenty infants, including 2 in whom congenital syphilis was detected, were kept under observation for at least one year. The following conclusions were drawn: 1. A positive neonatal blood test may simply reflect the existence of a positive reaction in the mother and is not of itself a criterion of syphilitic infection of the infant, nor is it an indication for treatment. A possible exception is a titer in excess of that of the mother, which may indicate syphilis in the infant. 2. Infants who were born of syphilitic mothers and who have positive neonatal blood tests are more likely to show subsequent evidence of congenital syphilis than infants with negative blood tests. 3. The diminution in strength of, or the disappearance of, the early positive reaction does not necessarily mean freedom from infection. 4. A strongly and consistently positive reaction between the third and fourth months after birth at full term points to congenital syphilis. 5. Two or more strongly positive reactions after a negative test point strongly to actual infection. 6. Unless a diagnosis of congenital syphilis has already been established, every infant born of a syphilitic mother should have periodic examinations, including efficient blood tests, for at least six months and preferably for one year. RAUH, Cincinnati.

SUBACUTE MILIARY PULMONARY TUBERCULOSIS WITH LARYNGEAL LOCALIZATION IN A TWO YEAR OLD CHILD. C. NOTO-CAMPANELLA, Med. ital. **1**:34 (Jan.) 1939.

A child with miliary tuberculosis showed at autopsy tuberculosis of the larynx. Noto-Campanella points out the difficulty of making a diagnosis of pulmonary tuberculosis without a tuberculin test and a roentgenogram. He points out the rarity of miliary tuberculosis with laryngeal localization in infants. Fifteen cases are reported in the literature. MARTOCCIO, Brooklyn.

TUBERCULIN PAPER TEST AND MANTOUX TEST. M. YAMADA and C. SATOMI, Acta pædiat. japon. **44**:1977 (Dec.) 1938.

The observers made tuberculin tests on 287 school children, first by the paper method of Hiro and one week later by intracutaneous injection of tuberculin according to the method of Mantoux. The paper test, simple to apply and giving 30 per cent positive reactions, in contrast to 33 per cent by the Mantoux method, is recommended for routine clinical use. KATO, Chicago.

PHOSPHOTUNGSTIC TUBERCULIN. Y. MIYAJIMA, Orient. J. Dis. Infants **24**:373 (Nov.) 1938.

Tubercle bacilli of the human and the bovine type were cultured in Sauton's albumose-free medium for eight weeks, and a tuberculin was obtained from the filtrates by means of sulfuric acid and phosphotungstic acid, according to the method of Boquet and Sauton. As compared with old tuberculin, this new tuberculin shows a similar degree of sensitivity in tuberculous guinea pigs, the bovine form showing a slightly greater sensitivity. The minimal lethal dose of this tuberculin is much greater than that of the old tuberculin. This new tuberculin is resistant to the action of ultraviolet rays but becomes decomposed rapidly (twelve hours) in the presence of a proteolytic ferment (pepsin or trypsin). Phosphotungstic tuberculin is readily adsorbed by animal charcoal, losing its potency completely in three hours.

KATO, Chicago.

TUBERCULOSIS OF THE KNEE JOINT. T. WALHEIM, Hygiea **100**:11 (Jan. 15) 1938.

Walheim reports a follow-up study of 143 patients (children as well as adults) treated for tuberculosis of the knee joint in the period from 1920 to 1934. At reexamination in 1935 9 patients were found to be dead—4 of phthisis, 2 of meningitis and 2 of amyloidosis. No necropsy was done on the 2 patients who died of amyloidosis. Two thirds of the patients were treated conservatively; one third, surgically. Of the former group, 38.5 per cent were healthy; in 16.9 per cent the condition was ameliorated; in 30.8 per cent the result was as yet uncertain, and in 13.8 per cent the result was bad. For those who were operated on, the corresponding figures were 70.3, 24.3, 5.4 and 0. The surgical treatment is therefore considered to be superior to the conservative one.

WALLGREN, Göteborg, Sweden.

PRIMARY TUBERCULOUS INFECTION OF THE SKIN. N. DANBOLT, Norsk mag. f. lægevidensk. **99**:44 (June) 1938.

The patient was a girl of 12 years. She suffered a traumatic lesion of the left elbow, and two weeks later the lymphatic glands of the axilla swelled. The lesion did not heal. Five weeks after the trauma erythema nodosum appeared. The Pirquet test was positive. There was fever for some weeks. The ulceration healed eventually, but at the site lupus developed. This was extirpated at the dermatologic clinic. Histologic examination showed tuberculosis.

WALLGREN, Göteborg, Sweden.

EPIDEMICS OF TUBERCULOSIS AND THEIR PREVENTION. E. FORSGREN, Svenska läk.-tidning. **35**:92 (Jan. 21) 1938.

Forsgren describes some local epidemics of tuberculosis produced by phthisic newcomers among groups of people who previously had been free from tuberculosis. Among fishermen's families on an island off the west coast of Sweden, a consumptive sailor was the source of infection in 20 cases of erythema nodosum, pleurisy, pulmonary infiltrations and phthisis. An epidemic in a school was traced to a substitute teacher. This man coughed and was examined by a physician, with a negative result, but later a roentgen examination disclosed cavernous pulmonary tuberculosis. Eighty per cent of his 37 pupils were found reactive to tuberculin (average percentage of reactors in the other schools of the district, 10 to 15 per cent). Sixteen of the children had signs of fresh tuberculosis, several acquired erythema nodosum, and 8 had to be sent to a sanatorium.

WALLGREN, Göteborg, Sweden.

AN EPIDEMIC OF BOVINE TUBERCULOSIS. G. OLSSON, Svenska läk.-tidning. **35**:101 (Jan. 21) 1938.

Fifty-eight persons, mostly children, who had taken unpasteurized milk from a farm where the herd gave evidence of infection fell ill within a short period

with signs and symptoms of fresh tuberculosis. Twenty-one of the patients had tuberculous manifestations of such a character (fever, lymphoma of the neck, tuberculosis of the mesenterial glands, erythema nodosum) that they needed treatment in a hospital. Bovine tubercle bacilli were demonstrated in the milk.

WALLGREN, Göteborg, Sweden.

A CASE OF TUBERCULIDES. G. LJUNGBERG, Svenska läk.-tidning. **35**:2080 (Dec. 16) 1938.

Papulonecrotic tuberculids were observed in a boy of 10 years suffering from tuberculous iritis. The incidence of tuberculids in patients admitted to the Children's Hospital of Göteborg, Sweden, has been much less during the last ten years than previously.

WALLGREN, Göteborg, Sweden.

## Diseases of Blood, Heart and Blood Vessels and Spleen

SPLENECTOMY IN THE TREATMENT OF PROVED SUBACUTE BACTERIAL ENDOCARDITIS. D. POLOWE, Arch. Surg. **38**:139 (Jan.) 1939.

A case is reported in which a cardiac ailment, proved to be subacute bacterial endocarditis, was treated by splenectomy. The literature is reviewed with regard to the use of this method of treatment. All of the patients previously reported to have been treated by splenectomy died, but the author's patient, a girl of 12 years, was well twenty months after splenectomy. The organism reported found in the blood stream was Streptococcus viridans.

KAISER, Rochester, N. Y.

RECOGNITION OF COARCTATION OF THE AORTA (ADULT TYPE) DURING CHILDHOOD. G. EISENBERG, J. Pediat. **13**:303 (Sept.) 1938.

Coarctation of the aorta is diagnosed infrequently in children. The classic findings of pulsating vessels of the thoracic wall and erosions of the ribs, seen in the roentgenogram, are obtained as a rule only for adults, for these abnormalities develop over a period of many years. Two clinical signs, however, may be of great aid in the diagnosis of coarctation of the aorta in children: (1) absence of femoral pulsations and (2) blood pressure higher in the arms than in the legs. Normally the reverse is present. Eisenberg includes brief histories of 3 cases of coarctation of the aorta in children. The patients were aged 2½, 3 and 9 years. In 2 of the cases the diagnosis was made on the basis of absence of the femoral pulsations and inability to obtain blood pressure measurements in the lower extremities.

RAUH, Cincinnati.

ACUTE LYMPHATIC LEUKEMIA (REPORT OF CASE SHOWING UNUSUAL NUMBER OF MONOCYTES). H. C. THOMPSON JR., New York State J. Med. **38**:1437 (Nov. 15) 1938.

A girl aged 2 years showed a rise in temperature, necrosis of the upper gums with sloughing, moderate cervical adenitis and a very large spleen. She had been ill for six days. Smears from the mouth contained spirillas and fusiform bacilli. The white cell count was 388,000, with 4 per cent monocytes. In three days the white cell count dropped to 35,000, and the monocyte percentage increased to 54.5. The condition was at one time considered monocytic leukemia but later was diagnosed as acute lymphatic leukemia. The child died on the twelfth day. In the discussion Dr. Doust presented a similar case.

AIKMAN, Rochester, N. Y.

PLATELET STUDIES IN MENSTRUATION AND HEMOPHILIA: TOTAL AND DIFFERENTIAL COUNTS, DISINTEGRATION RATES AND LIPID DISTRIBUTIONS. P. LEE and B. N. ERICKSON, Proc. Soc. Exper. Biol. & Med. **39**:264 (Nov.) 1938.

Five women were studied during menstruation with regard to the platelet count and the rate of disintegration of the platelets; also 9 hemophilic children. The platelets were differentiated into three groups according to their size in relation to the size of the red cell as a standard. Group 1 is one-fourth the size of the red cell; group 2, one-third; group 3, one-half. The nonmenstruating women had a decided decrease in both groups 1 and 2, while the hemophilic children showed a decrease in group 1 and a marked increase in group 2. A definite delay in the rate of platelet disintegration during menstruation is demonstrated by these studies. Hemophilia also is characterized by a slower rate of platelet disintegration. Analysis of platelets for lipids demonstrates no deficiency of cephalin during either menstruation or hemophilia. HANSEN, Minneapolis.

TREATMENT OF HEMORRHAGIC DIATHESES WITH VITAMIN C. G. WALTHER, Med. Klin. **34**:1327 (Oct. 14) 1938.

After a discussion of his disagreement with Winckelmann, who in an article in the current volume of this journal emphasized that vitamin C should be regarded as a food rather than as a medicament, Walther discusses vitamin C therapy for hemorrhagic diatheses and concludes that despite correction of vitamin C deficiency the hemorrhagic condition remains uninfluenced in many cases.

SIEMSEN, Chicago.

TREATMENT OF RHEUMATIC ENDOCARDITIS. H. MAY, Med. Klin. **34**:1386 (Oct. 14) 1938.

Prolonged rest is of prime importance, and the blood sedimentation rate is a good guide in determining how long rest should be continued. A second important maxim is that activity should be resumed gradually to avoid circulatory failure. Eradication of foci of infection is important, and this must not be limited to tonsillectomy. Recrudescence must be avoided as much as possible. An ordinary cold may mean recrudescence in a person with rheumatic heart disease.

SIEMSEN, Chicago.

ACUTE HEMOLYTIC ANEMIA (TYPE LEDERER). W. BRENNER, Ztschr. f. Kinderh. **60**:405 (Dec. 19) 1938.

In a boy 7 years old there developed quite suddenly severe hyperchromic anemia with evidence of destruction and rapid regeneration of blood, leukocytosis, anhepatic icterus and abdominal pain. Clinical improvement was followed ten weeks later by a more severe attack, accompanied by vomiting and a high remittent fever. Transfusions caused temporary improvement, but tonsillectomy and adenoidectomy were followed by permanent cure. The case corresponds to those described by Lederer (3 in 1925 and 3 in 1930). Eleven similar cases have been described, only 1 in the German literature.

As regards causes, infection is apparently an important factor. Allergy may play a role. Brenner thinks a constitutional factor may also be involved. His patient presented a tower head. This condition is common in association with familial hemolytic anemia. However, the diagnostic blood findings of this condition were absent in Brenner's case. SIEMSEN, Chicago.

AGE VARIATION IN FIBRINOGEN AND SEDIMENTATION RATES AFTER INJECTION OF COLLOIDAL SILVER. K. MURAKAMI, Acta pædiat. japon. **44**:1853 (Dec.) 1938.

Colloidal silver injected intravenously into young and adult rabbits caused a temporary acceleration of the sedimentation rate of each group, accompanied by an

increase in the fibrinogen content of the blood. This effect is more marked in adult than in young rabbits, and is explained on the basis of a greater functional activity of the reticuloendothelial apparatus in the young ones. KATO, Chicago.

ISOLATED CHRONIC MYOCARDITIS. LINDBERG, Finska läk.-sällsk. handl. **81**:114 (Feb.) 1938.

An 11 month old bottle-fed rachitic boy had suffered from whooping cough at 7 months and fever during one week at 9 months. He died rather suddenly with acute otitis. At necropsy chronic progressive myocarditis of a peculiar type was found: there were extensive, principally periarterially localized foci in which the muscle fibers had disappeared; these areas of the parenchyma were changed into edema-filled cavities and eventually transformed into scars of connective tissue. There was only very slight cellular reaction. The myocarditis is regarded as having been caused by one of the infections from which the infant had suffered.

WALLGREN, Göteborg, Sweden.

GANGRENE OF THE RIGHT ARM CAUSED BY LOCALIZED ARTERITIS OF OBSCURE ORIGIN. T. G. NYSTRÖM, Finska läk.-sällsk. handl. **81**:786 (Aug.) 1938.

A girl of 7 years had gangrene of the distal part of her right arm, which had manifested itself with increasing symptoms four months previously. No causes were demonstrable—no traumatic lesion, no infectious disease, no hereditary factor. The arm had to be amputated. Recovery followed. Exploratory arteriotomy revealed localized inflammation of the right brachial artery.

WALLGREN, Göteborg, Sweden.

A CASE OF RETICULOENDOTHELIOSIS. A. WALLGREN, Nord. med. tidskr. **15**:584 (April 15) 1938.

An infant, first seen at 4 months of age, had seborrheic dermatitis at 1 month of age and progressive anemia at 3½ months. At examination she had fever, enlargement of the liver and spleen, anemia (hemoglobin content, 32; red blood corpuscles, 1,460,000; white cells 12,300, with a slight shift to the left), numerous petechiae in the skin and in the visible mucous membranes, especially at the site of the dermatitis, and circular defects of the cranial vault. The child died one and one-half weeks later. Hand-Schüller-Christian disease was suspected, but the age of the child, the clinical signs and the low blood cholesterol (75 mg. per hundred cubic centimeters) made the diagnosis reticuloendotheliosis more probable. The histologic examination confirmed this suspicion.

WALLGREN, Göteborg, Sweden.

A CASE OF PAROXYSMAL TACHYCARDIA. A. WALLGREN, Nord. med. tidskr. **15**: 586 (April 15) 1938.

A boy of 4 had attacks of paroxysmal tachycardia (maximal rate of heart beat, 200) dependent on aberrant irritation of the sinus node or of the perisinal arc of the right auricle. The cause is unknown. On examination the heart appeared normal. During the attacks enlargement of the liver occurred. The attacks showed decreasing frequency and intensity.

WALLGREN, Göteborg, Sweden.

HEMOGLOBINOMETRY. A. R. MEYER, Nord. med. tidskr. **15**:712 (April 30) 1938.

With a standardized Zeiss-Icon hemoglobinometer, it was found that the lower limit of the normal hemoglobin content of the blood of hospitalized children was 80 per cent at 2 to 4 years of age and 85 per cent at 4 to 14 years of age.

WALLGREN, Göteborg, Sweden.

DISSECTING ANEURYSM OF THE THORACIC AORTA WITH SPONTANEOUS RUPTURE IN A BOY OF FOURTEEN. K. HARSTAD, Norsk mag. f. lægevidensk. **99**:1311 (Dec.) 1938.

A boy who previously had suffered from pneumonia but otherwise had been healthy was suddenly taken ill with violent paroxysmal abdominal pains radiating to the left scapular region and to the lower part of the thorax, vomiting and schock. No clinical diagnosis could be made, and even an exploratory laparotomy did not reveal any disorder. The boy died fourteen hours after the onset of the symptoms. He became suddenly extremely pale and then collapsed. At autopsy two ruptures of the middle part of the thoracic aorta due to dissecting aneurysm were found. There was perforation into the left pleural cavity, which contained 1,000 cc. of blood. There were no pathologic changes in the internal organs except slight hypertrophy of the left ventricle. Histologic examination of the aortic wall displayed no changes. The cause of the aneurysm is obscure (the Wassermann test was negative).

WALLGREN, Göteborg, Sweden.

A DANISH FAMILY WITH CONSTITUTIONAL OVALOCYTOSIS. A. BERTELSEN, Ugesk. f. læger **100**:136 (Feb. 10) 1938.

After a short summary of the 10 previously known instances of familial ovalocytosis, a description is given of a 3 year old boy with ovalocytosis and anemia. His brother, who had always been strkingly pale, died suddenly at the age of 8 months. The 3 year old boy was first seen two months before admission to the hospital. He had suffered from fever. The hemoglobin was 60 per cent. His skin was a pale yellowish color. He had marked splenomegaly and hepatomegaly. In the hospital the hemoglobin was 40 per cent and the red blood corpuscles numbered 2,900,000 and the white cells 2,400 per cubic millimeter. He had fever. After a blood transfusion he recovered rather rapidly. The enlargement of the spleen and liver and the ovalocytosis, however, remained unchanged. A catarrhal infection brought about a new, temporary decrease of the blood values. Some of the round red cells had a diameter of only 3.8 microns. The ovalocytosis occurred in 60 per cent of the red corpuscles. The mother, the father of the mother and the mother of the mother's father had ovalocytosis. In all, 12 of 21 members of this family followed through three generations showed ovalocytosis.

WALLGREN, Göteborg, Sweden.

MENINGOENCEPHALITIS IN INFECTIOUS MONONUCLEOSIS. V. SCHMIDT and A. NYFELDT, Ugesk. f. læger **100**:336 (March 31) 1938.

Schmidt and Nyfeldt report 5 cases in which meningoencephalitis developed in connection with infectious mononucleosis. Two of the patients were children, 16 and 14 years of age. The first child showed neurologic signs—stiffness of the neck and Kernig's sign. The spinal fluid of both children showed pleocytosis, principally lymphocytes, and increased globulin. The blood picture was typical. Recovery took place in about one month.

WALLGREN, Göteborg, Sweden.

HAND-SCHÜLLER-CHRISTIAN DISEASE. E. WARBURG, Ugesk. f. læger **100**:749 (July 7) 1938.

The patient was a hypotrophic girl of 8 years, of a healthy family. The first symptoms appeared at the age of 4. At that time she complained of pains in her legs, and a roentgenogram disclosed an area of localized destruction of the ilium. Later similar areas of localized destruction were found in the skull. Biopsy of matter from the ilium suggested myeloma. The clinical and roentgenologic diagnosis was, however, xanthomatosis. Later, destruction was noted in the right tibial bone. There was no hepatomegaly. The spleen was not enlarged. There was no exophthalmos. The cholesterol content of the blood was 217 mg. per

hundred cubic centimeters. The hemoglobin content was 100 per cent. The Wassermann reaction was negative. A tuberculin test was negative. Later, polyuria developed. The child was treated with roentgen rays, with some amelioration of the condition.

WALLGREN, Göteborg, Sweden.

MONOCYTIC LEUKEMIA. P. PLUM and S. THOMSEN, Ugesk. f. læger **100**:755 (July 7) 1938.

A boy of 11 years became ill with a high fever and an eruption of scanty large vesicular efflorescences. At examination he was found to have, besides fever and the eruption, enlargement of the lymph nodes of the neck. The liver and spleen were not palpable. The blood culture was sterile. The hemoglobin content was 66 per cent. The white blood cell count was 525, with 15 per cent. granulocytes (3 per cent segmented), 49 per cent lymphocytes, 9 per cent monocytes and 27 per cent unclassified mononuclears. The last cells were of the same size as monocytes but had more basophilic cytoplasm. The nucleus was globoid and contained up to four nucleoli.

The bullous eruption progressed and finally involved most of the skin. The new vesicles were hemorrhagic. At the slightest trauma of the skin the epidermis was loosened. The white blood cell count increased to 30,000, with an increase in the number of large monocytic cells (90 per cent). The liver, spleen and lymph nodes showed clinically no changes. The fever continued. The boy died ten days after the beginning of the disease.

Postmortem examination showed: hyperplasia of the lymph nodes, spleen and bone marrow; degeneration of the liver and kidneys, and bronchopneumonia. Microscopic examination revealed monocytic pneumonia, large agglomerations of monocytic cells in the skin, and abundant monocytes of various sizes in the bone marrow. There was no infiltration of the liver and spleen.

WALLGREN, Göteborg, Sweden.

SEDIMENTATION CURVES OF THE BLOOD. A. J. F. OUDENDAL, Nederl. tijdschr. v. geneesk. **82**:5863 (Dec. 10) 1938.

The blood sedimentation test carried out by the micromethod of Burger (1930) gives reliable results in practice when resorted to in addition to the more usual methods of blood examination. The progress of sedimentation can be laid down in a curve, indicating the speed per minute as determined over periods of fifteen minutes during the first hour and of thirty minutes during the second. Routine tracing of these sedimentation curves permits a comparison of the changes in the blood plasma during the progress of an illness with the changes in the morphologic elements of the blood in the same patient.

VAN CREVELD, Amsterdam, Netherlands.

RESEARCHES ON THE CIRCULATION OF BLOOD IN CLUBBED FINGERS. W. H. D. DE HAAS, Nederl. tijdschr. v. geneesk. **83**:384 (Jan. 28) 1939.

By means of comparative investigations (microscopic examination of capillaries; estimations of venous pressure and of cutaneous temperature) in two groups of subjects suffering from bronchiectasis, one with and the other without clubbing of the fingers, de Haas demonstrates that in clubbed fingers the smallest vessels are not dilated but narrowed.

VAN CREVELD, Amsterdam, Netherlands.

DETERMINATION OF COAGULATION TIME BY MEANS OF THE INTENSITY OF LIGHT PASSING THROUGH THE BLOOD. H. FESTEN, Nederl. tijdschr. v. geneesk. **83**:396 (Jan. 28) 1939.

Festen devised a method for estimating accurately the coagulation time of blood and plasma. This method is quite simple: Light from a constant source is pro-

jected through the blood during the process of coagulation; the opacity caused by the formation of fibrin decreases the amount of light projected through the blood—a decrease which can be observed and registered. The advantage of this method is the possibility of being informed as to the onset of coagulation and as to the entire progress of coagulation without the blood or plasma being interfered with during the whole period.

VAN CREVELD, Amsterdam, Netherlands.

A SIMPLE COLORIMETRIC METHOD FOR DETERMINING THE OXYGEN SATURATION OF THE BLOOD. J. H. P. JONXIS, Nederl. tijdschr. v. geneesk. **83**:876 (Feb. 25) 1939.

This method is founded on the difference in the absorption of violet rays with a wavelength of 536 millimicrons by hemoglobin and oxyhemoglobin. The absorption by the hemoglobin is three times as great as that by the oxyhemoglobin, whereas the absorption of light by both substances runs parallel to their concentration. A normal plunger colorimeter may be used.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Nose, Throat and Ear

SOME ETIOLOGIC FACTORS IN THE PATHOLOGY OF STAMMERING. I. LATIF, Brit. J. M. Psychol. **17**:307 (Dec.) 1938.

Latif finds that claims to one universal treatment in all cases of stammering are not justified by results and that, whereas some disorders of speech yield to one kind of treatment, a large number remain unaffected by it. The author attempts an analysis of a few etiologic factors in the onset and cure of stammering by presenting 2 cases. These cases illustrate the observation that the causes of stammering and its treatment vary from one case to another. The first case shows that although stammering may have its inception in factors (fear of parents, sense of guilt because of masturbation, inferiority, imitation and fear of a stammering heredity) which may be regarded as more or less primary, other conditions, such as lack of steady control over breathing and voice and faulty habits of reading, may further complicate the etiologic factors in the disorder during the course of its development. Consequently, no therapeutic measure can be really effective unless, with the primary factors, it takes into account secondary conditions. Besides the analysis of the second patient's difficulties (which were similar to those of the first) when he was in a state of relaxation, the author also tried a few exercises of musical drill with him. In addition to this, he assigned a few tasks requiring delicate handling of instruments in the laboratory in order to help the patient overcome his sense of inadequacy in manual skill. The period of treatment lasted over eleven months, after which the patient was completely cured. Oral or phonetic exercises were not resorted to during the entire course of treatment.

J. A. M. A.

DERMOGRAPHIA IN PATIENTS WITH ADENOIDS. C. CALABRESI, Arch. ital. di otol. **51**:94 (Feb.) 1939.

Previous studies of dermographia have led to false deductions, because the methods of investigation have been inaccurate. Contrary to previous opinions, Calabresi regards this reaction as a physiologic phenomenon. Recent investigations tend to place dermographic reactions in the field of the neuroendocrine and the neurovegetative system, the index of sympathetic excitability being vasoconstriction, and of parasympathetic excitability, vasodilatation. Symptoms of functional alterations in the neurovegetative system in children with adenoids led Calabresi to examine the dermographic reflex in such patients. Using Comel's apparatus, by which the pressure is accurately determined, he examined 114 subjects. The

results of the examination were not conclusive, since in normal controls he found great variations in the reaction. The most that can be said is that in the subjects studied the neurovegetative system manifested a certain liability.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

CROUP DUE TO DIPHTHERIA AND TO FOREIGN BODIES. H. OPITZ, Kinderärztl. Praxis **9**:518 (Dec.) 1938.

Opitz reports one of his own cases in which diphtheria was diagnosed as the cause of croup. Five days after tracheotomy had been performed, the cannula could not be removed without reappearance of the symptoms of croup. Roentgenograms revealed a splinter of bone just above the cannular shadow.

The differential diagnosis between diphtheritic croup, pseudocroup and croup due to foreign body is discussed.

Diphtheritic croup does not start suddenly but becomes worse slowly and steadily. Hoarseness increases to aphonia. The child is usually ill for days before the croup develops. The temperature is often only slightly elevated.

Pseudocroup has an acute onset, chiefly at night, and is accompanied by a barking cough. The voice is never completely aphonic. The intensity of the croup varies; it is usually better during the day and becomes worse at night. The temperature is usually high. Repeated attacks are characteristic within the first years of life.

Croup due to foreign body also starts with an acute onset. Symptoms of the first aspiration are generally alarming but are soon followed by amelioration. Slight cyanosis and labored, shallow and rapid breathing often persist, however, and hoarseness develops on account of swelling of the mucous membranes. The temperature at first is normal but often rises on the second day. Roentgenograms help in the diagnosis if a shadow shows the foreign body. Tracheotomy should be performed if asphyxia is threatening. Also it may prevent further descent of the foreign body into the bronchial tree.

HEYMANN, Cleveland.

FATAL SPONTANEOUS HEMORRHAGE FROM A TONSIL. E. SCHLITTLER, Pract. oto-rhino-laryng. **2**:19 (Feb.) 1939.

Schlittler reports a case of spontaneous hemorrhage from one tonsil, apparently due to erosion by phlegmonous necrotic inflammation.

The patient, in spite of this condition, did not show any evidence of generalized infection or toxemia. Microscopic examination of the tonsillar bed showed extreme alteration of the smaller blood vessels within the necrotic area, but the author was not able to see any evidence of erosion of the larger arteries or veins.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

HEMANGIOMA OF THE TRACHEA. LOTAR HOFMANN, Ztschr. f. Hals-, Nasen- u. Ohrenh. **44**:435, 1938.

The author reports hemangioma of the trachea in 2 infants, each 2 months old. The symptoms, the clinical course and the pathologic picture were practically identical in both. The peculiar type of stridor was characteristic of a laryngeal obstruction and seemed to improve on quiet respiration or sleep but became worse during any excitement or crying spell. The diagnosis was suggested by direct laryngoscopic examination. In addition, the author found evidences of hemangioma in other sites of the body.

He suggests local treatment and perhaps roentgen therapy or surgical intervention, but he doubts their value, since bronchitis and pneumonia may occur early and terminate the case.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

MÉNIÈRE'S SYNDROME ON ALLERGIC BASIS? G. MUHL, Nord. med. tidskr. **15**: 582 (April 15) 1938.

A girl of 3¾ years had previously had atopic eczema and strophulus. She had suffered from frequent attacks of Ménière's syndrome since she was 2½ years of age, lately alternating with Quincke's edema of the eyelids. She was probably allergic to some vegetables.

WALLGREN, Göteborg, Sweden.

## Diseases of Lungs, Pleura and Mediastinum

ATELECTASIS OF THE LUNGS OF A NEWBORN BABY RESULTING FROM LESIONS OF THE NERVE CENTERS. R. DETRÉ, J. MARIE, M. LAMY and DE FONT-RÉAULX, J. Pediat. **13**:208 (Aug.) 1938.

A newborn premature infant suffered from respiratory disturbance beginning on the seventh day of life. The symptoms increased in intensity, and a roentgenogram demonstrated atelectasis of the right lung. The infant died at the age of 59 days. At no time were there any symptoms referable to the central nervous system. At autopsy, in addition to atelectasis of the lung, a large hematoma was found in the bulboprotuberential region, due to a meningeal peribulbar median hemorrhage. Three other cases of atelectasis in newborn infants are briefly reviewed. One of the infants died, and no examination of the brain was made; the other 2 recovered. The question is raised as to whether the origin of the atelectasis may not be found in the central nervous system. A discussion of the nervous mechanism of atelectasis is presented. The authors believe that in certain cases atelectasis, apnea and serious disturbances of the respiratory rhythm of the newborn or young infant have been caused by a meningeal hemorrhage.

RAUH, Cincinnati.

SERUM TREATMENT OF PNEUMONIA IN CHILDHOOD. R. L. NEMIR, J. Pediat. **13**:219 (Aug.) 1938.

This is a report on 69 infants and children treated with antipneumococcus serum and 128 untreated patients observed during the period from Sept. 15, 1933, to June 1, 1936. The types of Pneumococcus causing the pneumonias for which serum was used were I, II, IV, V, VI, VII, IX, XIV, XVIII and XIX. Types I, XIV and VI were the predominant organisms associated with lobar pneumonia, accounting for almost half of the cases of lobar pneumonia in this series. Type I pneumococcus was the predominant organism in the older children and type XIV in the infants less than 2 years of age. The untreated control group included more mildly ill patients than the treated group. The mortality rate for lobar pneumonia was low in both groups, and in this small series the administration of serum effected no reduction. The incidence of empyema in patients with lobar pneumonia due to types I, XIV and V who were receiving serum early in the disease was reduced. Late administration of serum in severely ill patients was valueless in preventing or reducing the development of this complication. A dramatic precipitation of the crisis was observed in the majority of patients treated with specific antibody within twelve to eighteen hours after the first treatment. The author advises the use of antipneumococcus serum only in the treatment of those patients who are severely ill and in whom the diagnosis is made early and in the treatment of young infants, in whom the mortality rate is high.

RAUH, Cincinnati.

OBSERVATIONS ON SULFANILAMIDE THERAPY IN PNEUMONIA AND MENINGITIS DUE TO TYPE 3 PNEUMOCOCCI. J. F. SADUSK JR., New England J. Med. **219**:790 (Nov. 17) 1938.

Two fatal cases of type 3 pneumococcus meningitis are described in which sulfanilamide was administered. In both cases the blood cultures made prior to

treatment were positive, while those made after the institution of sulfanilamide therapy were sterile. In 1 case the spinal fluid also had been sterilized.

Nine patients of 53 years of age and above, save 1 who was 18, were treated for type 3 pneumococcus pneumonia with sulfanilamide. All these patients recovered and were discharged from the hospital in good condition.

Sadusk suggests the further use of sulfanilamide in the treatment of patients with type 3 pneumococcus infections in order that more data may be obtained for analysis.

GENGENBACH, Denver.

SEVERE ANEMIA AND HEMATEMESIS IN A CHILD WITH CHRONIC NONTUBERCULOUS PULMONARY DISEASE. B. WEILL-HALLÉ and S. LOEWE-LYON, Bull. Soc. pédiat. de Paris **36**:384 (June) 1938.

An 18 month old boy, somewhat undernourished, coughed and had signs of disease in the left lung, which were interpreted as due to unresolved bronchopneumonia or bronchiectasis. The tuberculin test was negative. Repeated hematemesis occurred. He became anemic to a greater extent than could be explained solely on the basis of hemorrhage. The pulmonary infection was thought to have an etiologic bearing on the anemia. The Wassermann reaction of the blood was negative. The anemia improved following administration of iron, liver extract and abundant vitamins.

BENJAMIN, Montreal, Canada.

CLINICAL ASPECTS OF BRONCHIECTASIS. R. HERBST, Med. Klin. **34**:1352 (Oct. 14) 1938.

A congenital predisposition is probably present in most cases of bronchiectasis. Supposedly this condition is most common in the lower lobe of the left and upper lobe of the right lung and in the bronchus cardiacus. Injury (infectious or mechanical) is also of etiologic importance. Stagnation of secretions and infection enhance the progress of bronchiectasis. In the absence of bronchitis bronchiectasis may be symptomless for years. In the presence of infection the clinical picture is characterized by a paroxysmal cough with voluminous expectoration. The sputum, which settles into three layers, contains a variety of bacteria. An acid-fast pseudotubercle bacillus may lead to diagnostic errors, and a culture is frequently advisable. The offensive odor of the sputum is supposedly due to anaerobes. Hemoptysis is more common than with tuberculosis. On physical examination coarse moist rales are characteristic. Roentgenographic examination without contrast material may yield negative results. Tomography is a recent aid.

Treatment must be directed at the bronchitis and toward diminishing the secretion. Postural drainage is helpful. In cases in which congenital bronchiectasis of the lower lobe of the left lung becomes manifest in the young person, extirpation of the entire lobe has become increasingly successful.

SIEMSEN, Chicago.

PLEURAL EMPYEMA CAUSED BY BACILLUS MEGATHERIUM. A. GREVILLIUS and K. QUARNÅ, Hygiea **100**:737 (Oct. 15) 1938.

Postpneumonic pleural empyema occurred in a 1½ year old infant. Recovery followed operation. In the pus Bacillus megatherium was demonstrated.

WALLGREN, Göteborg, Sweden.

PULMONARY SARCOMA IN AN INFANT OF THREE WEEKS. G. GEZELIUS, Svenska läk.-tidning. **35**:2004 (Dec. 2) 1938.

A newborn infant began to suffer from respiratory difficulties at the age of 3 weeks. At examination, one week later, there were cyanosis, dyspnea and physical signs of infiltration of the right lung. A tuberculin test was negative. The temperature was 38 C. (100.4 F.). The symptoms progressed, and the child

died three days after admittance to the hospital. A large lobular tumor of the caudal lobe of the right lung was found at postmortem examination. Histologic examination showed sarcoma.

WALLGREN, Göteborg, Sweden.

METAPNEUMONIC ABSCESS OF THE LUNG. G. GEZELIUS, Svenska läk.-tidning. **35**:2005 (Dec. 2) 1938.

Gezelius reports large benign metapneumonic pulmonary abscesses in a girl 12 and a boy 1¾ years of age. In the girl the pulmonary disease cleared up totally; in the boy there remained an air-filled cavitation at the base of the left lung (emphysematic bleb?).

WALLGREN, Göteborg, Sweden.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CELIAC DISEASE AND ITS ULTIMATE PROGNOSIS. S. V. HAAS, J. Pediat. **13**:390 (Sept.) 1938.

Haas gives a brief historical review of celiac disease. He believes that celiac disease is due primarily to intolerance for a carbohydrate and can be cured by diet alone. He has treated 134 consecutive patients. In addition to control of the diet the only therapy used was the administration of vitamin D and sometimes iron. One patient died of pneumonia during the second week of treatment. Another died of essential nephrosis long after a cure had been effected. No other patients have died. One boy of 15 years is underweight and undersize. One patient proved to be diabetic. One adult, although generally well, is sensitive to carbohydrates and has an occasional loose stool. This patient probably has sprue. The remainder are alive and well. Seventeen patients have begun treatment too recently for data on them to be of value in this analysis, although all are progressing satisfactorily. The 8 patients for whom the diet was first used are healthy and normal after fifteen years. All are of normal height. Five are of normal weight or above. Three are underweight. All are on a full diet, and there have been no relapses. Of the remaining subjects, all are normal or above normal in height, and 86 are normal or above in weight.

The dietary principles which Haas has followed are: No milk as such may be used. No sugar or starch is to be taken in any form except as it occurs in bananas and oranges and in protein milk, calcium caseinate milk or cottage cheese. Protein may be taken in any form, as meat, egg white, gelatin, protein milk, calcium caseinate milk and cottage cheese. Vegetables, except potato, and fruits other than those named may be added to the diet after a long period. The restricted diet should be continued for at least a year. If the patient does not respond to this diet, the diagnosis is incorrect.

RAUH, Cincinnati.

RELATION OF INTESTINAL BLEEDING TO HETEROTOPIC GASTRIC MUCOSA AND ULCERATION IN MECKEL'S DIVERTICULUM. A. L. ABRAMS, J. Pediat. **13**:513 (Oct.) 1938.

Surgical and autopsy reports of Meckel's diverticulum at the Babies Hospital have been reviewed to elucidate the relationship of intestinal bleeding to the type of mucosa existing in the diverticulum and to the occurrence of ulceration in the mucosa. The results showed (1) that intestinal bleeding in patients with this clinical syndrome indicated the presence of heterotopic gastric mucosa but that in this series ulceration was rarely found, and (2) that heterotopic gastric mucosa was present in many of the patients with this condition and in a fair number occurred without intestinal bleeding.

RAUH, Cincinnati.

RUPTURE OF THE DUODENUM IN A THREE YEAR OLD CHILD. O. S. WYATT, Minnesota Med. **21**:792 (Nov.) 1938.

This report concerns a child of 3 years—probably the youngest on record—who was injured by an urn which fell on him. He complained of abdominal pain at

once, and a few hours later was seen by the writer of this report. The child gave evidence of an acute lesion of the abdomen calling for surgical treatment, and the presence of free bile caused the surgeon to suspect injury to the biliary apparatus or to the duodenum. There was found in the duodenum a longitudinal rent about 1.5 cm. in length, through which bile was escaping. The rent was closed, drainage established and the closure of the abdominal wall done in layers. The patient was given a transfusion while on the table. He was discharged on the twenty-fifth day, and three months after operation was found to be in perfect health. Wyatt points out that duodenal rupture is extremely rare and states that Rowland reported observing only 23 cases in a series of 381 cases of rupture of the intestines.

ANDERSON, Minneapolis.

ENZYMATIC BREAKDOWN OF GLYCOGEN IN LIVER EXTRACTS. G. T. CORI and C. F. CORI, Proc. Soc. Exper. Biol. & Med. **39**:337 (Nov.) 1938.

In previous papers (Cori, G. T.; Colowick, S. P., and Cori, C. F.: *J. Biol. Chem.* **123**:375, 1938; **124**:543, 1938) it was shown that dialyzed liver extracts contain an enzyme which forms dextrose-1-phosphoric acid (1-ester) from glycogen and inorganic phosphate and that this enzyme is activated by adenylic acid. When dextrose-1-phosphoric acid is added to liver extract, inorganic phosphate is split off, owing to the presence of a phosphatase. The liver of a fasting rabbit was extracted, dialyzed and treated with phosphate, adenylic acid and phlorhizin.

It is concluded that there is present in the dialyzed liver extract an enzyme system which after addition of phosphate buffer and adenylic acid is capable of rapid formation of dextrose from glycogen. It seems possible that the blood sugar of mammals is produced by this enzyme system rather than by diastase.

HANSEN, Minneapolis.

GALACTOSURIA AND LACTOSURIA IN DIARRHEAL DISEASES OF INFANTS. S. TAMURA, Acta pædiat. japon. **45**:93 (Jan.) 1939.

The results of 167 urinalyses with special reference to the passage of galactose and lactose in 42 infants with diarrheal diseases are presented. Galactosuria has a far better prognosis than lactosuria in this type of disease. KATO, Chicago.

RECURRENT INTUSSUSCEPTION. O. POVLSEN, Hospitalstid. **81**:481 (May 17) 1938.

A full term, breast-fed infant of 11 months had repeated attacks of intussusception, diagnosed roentgenologically and clinically. During the five months the disease lasted about 50 attacks were observed. Recovery occurred. Roentgenoscopic examination showed as the cause of the recurrent intussusceptions an abnormal liability to spastic contractions of the colon. Even a slight touch on the abdominal wall produced severe spasm of the colon. It is recommended that unnecessary replacement manipulations during conservative treatment with water enemas be avoided.

WALLGREN, Göteborg, Sweden.

NODULAR CIRRHOSIS OF THE LIVER AFTER ACUTE HEPATITIS. A. RAMHULT, Svenska läk.-tidning. **35**:871 (June 10) 1938.

At the Children's Hospital of Göteborg during the last ten years 5 patients have been observed in whom nodular cirrhosis of the liver appeared after an attack of acute hepatitis (catarrhal jaundice). Ramhult gives a brief report on the first 4 and a detailed report on the fifth. The latter was a boy of 7 who fell ill with catarrhal jaundice in the autumn of 1935. The jaundice disappeared after six weeks, but the patient continued to suffer from somewhat indistinct abdominal symptoms. He was admitted to the hospital because of melena. He was anemic, with hemoglobin 56 per cent. Examination showed, further, slight bilirubinemia,

purpuric spots on the rectal mucosa, nodular enlargement of the liver, no ascites, no ectasia of esophageal veins and no splenomegaly.

The first patient, a 14 year old boy, had acute hepatitis in April 1926 and cirrhosis in August. He died in October. The second, a boy of 13, had hepatitis in December 1927 and cirrhosis in August 1928. He died in September 1929. The third, a girl of 8, had hepatitis in December 1931 and cirrhosis in January 1932. She died in November 1933. The fourth, a girl of 9, suffered from acute hepatitis in May 1932. Cirrhosis was diagnosed in May 1933. She died Nov. 19, 1933. All those whose cirrhosis proved fatal were examined post mortem, with anatomic confirmation of the clinical diagnosis in each case.

WALLGREN, Göteborg, Sweden.

ACUTE ABDOMINAL PROCESSES. T. JANSSEN, Maandschr. v. kindergeneesk. **8**:150 (Jan.) 1939.

Janssen discusses the diagnostic difficulties in 4 cases in each of which acute abdominal symptoms were presented: (*a*) intussusception on which, wrongly, a diagnosis of dysentery had been made; (*b*) rheumatism with a severe abdominal disturbance; (*c*) a complex of symptoms that probably found its origin in the torsion of a coil of the ileum; (*d*) spasmodic contractions of the intestine without real peristalsis as part of the symptom complex in cyclic vomiting with acetonemia.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF ICTERUS INFECTIOSUS (WEIL'S DISEASE). S. C. MEYER, Maandschr. v. kindergeneesk. **8**:179 (Feb.) 1939.

An 11 year old girl sixteen months previous to her death suffered from an attack of acute jaundice or hepatitis infectiosa. Postmortem examination revealed cirrhosis of the Laennec type. Meyer stresses the point that icterus in hepatitis infectiosa lasting longer than three weeks is a danger signal, indicating acute hepatic necrosis or cirrhosis. One must not postpone the use of insulin in these cases.

VAN CREVELD, Amsterdam, Netherlands.

INTESTINAL INFECTION CAUSED BY LARVAE OF SARCOPHAGA HAEMORRHOIDALIS IN A CHILD. L. S. WILDERVANCK, Nederl. tijdschr. v. geneesk. **83**:756 (Feb. 18) 1939.

Intestinal myiasis in a boy of 2 years was caused by larvae of Sarcophaga haemorrhoidalis. The clinical symptoms were anorexia, abdominal pain, unquiet sleep, vomiting and diarrhea. About 30 larvae were voided with the stool, and recovery followed. The prescription of a harmless laxative is in most cases sufficient.

VAN CREVELD, Amsterdam, Netherlands.

## Nervous Diseases

A QUANTITATIVE STUDY OF THE NEWBORN AND ADULT SPINAL CORDS OF MAN. A. M. LASSEK and G. L. RASMUSSEN, J. Comp. Neurol. **69**:371 (Dec.) 1938.

A comparison of the spinal cord of the newborn with that of the adult was made on the spinal cords of 6 newborn infants and 6 adult Negroes by comparing measurements of the gray and the white substance of the four segments of the cord. In the adult the white substance formed 82.2 per cent of the total volume of the spinal cord. In the newborn it represented only 33 per cent. The thoracic region of the cord showed the greatest relative increase in length, area and volume between birth and maturity.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

HUMAN ENCEPHALITIS CAUSED BY THE VIRUS OF THE EASTERN VARIETY OF EQUINE ENCEPHALOMYELITIS. LER. D. FOTHERGILL, J. H. DINGLE, S. FARBER and M. L. CONNERLEY, New England J. Med. **219**:411 (Sept. 22) 1938.

During the summer of 1938 there was an epidemic of encephalitis among horses in Massachusetts. During this same period encephalitis occurred in a number of infants and children.

One patient, a 7 year old boy, was admitted to the Children's Hospital for an illness characterized by an abrupt onset of high fever, generalized rigidity and coma. The patient was extremely ill, with a temperature varying between 104 and 105 F. The cerebrospinal fluid showed 2,000 cells, 85 per cent of which were polymorphonuclear leukocytes, a normal concentration of dextrose and a total protein content of 190 mg. per hundred cubic centimeters. Bacteriologic cultures were negative. Generalized convulsions occurred, and the patient died about twelve hours after admission, forty-eight hours after the onset of his illness.

Postmortem examination of the child revealed acute encephalitis, severe edema and congestion of the brain and cord, generalized visceral congestion, early interstitial pneumonitis and pulmonary edema.

The virus of the Eastern type of equine encephalomyelitis was isolated and identified as the etiologic agent.

GENGENBACH, Denver.

EXPERIENCES WITH THE AMBRUS SPINAL FLUID COLLOID REACTION. S. STRNAD, Ztschr. f. Kinderh. **60**:428 (Dec. 19) 1938.

In 1933 and 1934 Ambrus reported a new diagnostic spinal fluid colloid reaction. The method has been applied as a routine at the Brunner Children's Hospital for four years, and 300 cases are reported. The reaction is classified as I, II, III or IV, according to its type, and the prognosis varies with the type. It also has differential diagnostic value. The test is simple, but the reagents must be fresh.

SIEMSEN, Chicago.

SUBARACHNOID BLEEDING IN CHILDHOOD. E. ENGELHARDT, Ztschr. f. Kinderh. **60**:436 (Dec. 19) 1938.

The clinical manifestations of subarachnoid hemorrhage are sudden in onset, like those of apoplexy. Lumbar puncture is diagnostic in that the first portion of spinal fluid withdrawn is less bloody than that withdrawn later. After one or more days have elapsed the fluid is xanthochromic. Lumbar puncture is of therapeutic value also.

The etiology is uncertain. Vascular defects, aneurysm, or increased vascular permeability due to deficiency of vitamin C may be factors. In the author's opinion the last was the cause in the case of an 11 year old boy reported by him. He thinks that the hematuria which the patient had previously was on the same basis.

SIEMSEN, Chicago.

POSTOTITIC HYDROCEPHALUS. E. JERLANG, Hospitalstid. **81**:1028 (Oct. 25) 1938.

Jerlang reports 3 cases of hydrocephalus in children 7 to 9 years of age. Two of the children recovered after repeated spinal punctures. In the third child a decompression trepanation had to be performed in order to save the sight. In addition a case of postotitic cerebral abscess is reported in which the symptoms and signs at the beginning were similar to those in the 3 cases of hydrocephalus. The hydrocephalus is regarded as due to a diminution in the absorption of the fluid, caused by thrombophlebitis. In cases in which thrombophlebitis can be excluded the hydrocephalus may be due to a toxic lesion of the meninges.

WALLGREN, Göteborg, Sweden.

ACCUMULATED CASES OF PFEIFFER MENINGITIS. A. WALLGREN, Nord. med. tidskr. **15**:585 (April 15) 1938.

During the ten year period from 1925 to 1934 Pfeiffer's meningitis was not encountered in Göteborg, while since that time the disease has been observed with increasing frequency. In all, 7 patient have been treated for it, all with a fatal outcome. This type of meningitis has not been observed in other parts of Sweden, and it has been seen in only a few instances in other Scandinavian countries.

WALLGREN, Göteborg, Sweden.

## Psychology and Psychiatry

PRACTICAL ASPECTS OF CHILD GUIDANCE. C. STEIN, New England J. Med. **219**:844 (Nov. 24) 1938.

The report attempts to answer the oft-repeated question "What price child guidance?" by presenting the results of six years of study, based on 500 children, all examined and treated by the same psychiatrist, in a single clinic serving a stable metropolitan community.

Two hundred and ninety-five (57 per cent) of the children were boys, and 205 were girls. One fifth were under 5 years of age, one third were between 5 and 10, one fourth were between 10 and 15 and one sixth were 15 or older (mostly under 17).

Forty-seven per cent presented problems of habit training, 27 per cent problems of education and retardation and at least 70 per cent emotional insecurity.

Incorrigible children (including spoiled children and children with emotional insecurity) head the list with 46 per cent.

The physical examinations indicated a very high proportion of removable defects in these children; this indicates that the role of pediatrics in the general practice of medicine is no less important than that of mental hygiene.

GENGENBACH, Denver.

THE CONTRIBUTIONS OF PSYCHOANALYSIS TO THE EDUCATION OF THE ADOLESCENT. C. B. ZACHARY, Psychoanalyt. Quart. **8**:98, 1939.

Zachary's thesis is that the fundamental purpose of education is to help the growing person to learn to face society as it is and to adjust himself to it, in order that he may be able to participate in satisfying ways and perhaps to change it. The adolescent is greatly in need of such an educational program because he is passing through the most profound transition of his life, because society gives less attention to education to fit the needs of the adolescent than it does to education of the elementary and nursery school child and because, although one of the major problems of the adolescent is to establish his adulthood, society tends to permit him to achieve this only if his doing so meets its needs at a given time.

There is no person who passes through adolescence without conflicts, and it is the duty of the school to help him deal with them rather than to add to them. This is particularly the task of the school in modern society, because adults in a civilized society do not give the special assistance to those approaching adulthood that adults in primitive societies do. Psychoanalysis makes special contributions to the education of the adolescent. 1. It can help educators to understand better the dynamics of classroom behavior. Its concepts of the development of personality can aid educators to observe the adolescent in all his activities and surroundings, including the unconscious drives behind his creative productions, so that they can appreciate more accurately the conflicts, needs and aspirations of the adolescent and understand better the personality and the struggles which lie behind the symptomatic behavior. 2. The analyst, because of his experience

in dealing intensively with maladjustments, is in the best position to interpret to teachers the behavior of adolescents who need special help and to give adequate short time guidance to the youths themselves.

PEARSON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

SOME GENETICAL PROBLEMS IN MENTAL DEFICIENCY. L. S. PENROSE, J. Ment. Sc. **84**:693 (Sept.) 1938.

The few diseases in which hereditary mental defect has been clearly demonstrated are found in idiots and imbeciles. Much less is known about the hereditary factors which underlie feeblemindedness. In all grades of mental defect, heredity plays an approximately equal part, but the degree of dominance of the hereditary factors is different in the various grades. The defects in idiots and imbeciles are often recessively determined or are due to fresh mutation, and are less obviously hereditary than those in simpletons, who, like normal persons, owe their mental grade to the interaction of dominant additive factors. Environmental influence may be the only cause in comparatively rare cases. External circumstances, indeed, are likely to be even more important in mild than in severe mental deficiency, for their effects may make the difference between certifiability and normality.

KASANIN, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

CONSANGUINITY AND MENTAL DISORDER. T. A. MUNRO, J. Ment. Sc. **84**:708 (Sept.) 1938.

Munro made an inquiry into the incidence of consanguineous parentage in the populations of hospitals for mental disease in seven English counties and in two cities, Cardiff, Wales, and Edinburgh, Scotland. The inquiry also included the examination of 152 patients with related parents and the comparison of them and of their families with a similar group of patients with unrelated parents selected at random from the populations of hospitals for mental disease.

Munro concludes that there is a definite specific familial incidence of mental disease. The relatives of patients with affective psychoses, when they are psychotic, tend to suffer from affective psychoses, and the relatives of schizophrenic patients suffer from schizophrenia. This specific familial incidence is true not only for the broad reaction types but also for each clinical type within the group, except the organic psychoses of exogenous origin. The more strict the criterion of manic-depressive disease in the patient, the more typically manic-depressive are the disordered relatives and the more definitely dominant is the inheritance. Famial incidence holds for the schizophrenias; it is most evident in the paranoid form and least evident in the catatonic form. The incidence of mental disorder among relatives decreases in an orderly way with the decreasing degree of relationship to the patient.

KASANIN, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

TAY-SACHS AMAUROTIC FAMILIAL IDIOCY: REPORT OF CASES. T. WERNCKE, Klin. Monatsbl. f. Augenh. **100**:665 (May) 1938.

The identity of the amaurotic familial idiocy of Tay-Sachs and of other forms of amaurotic famial idiocy, especially Niemann-Pick disease, is still disputed. The author reviews the literature in point and finds reported observations on about 15 eyes removed from patients who succumbed to Tay-Sachs disease. He adds to these data the pathologic observations on eyes removed post mortem from 4 children, aged 1 year and 8 months, 1 year and 1 month, 1 year and 3 months, and 2 years, respectively. The clinical and the pathologicoanatomic condition coincided in these 4 children, who were of Jewish parentage. The disease became manifest in the sixth month of life, and the children died at about the age of 2. All of the children were originally normal; they then ceased to develop, degenerated, lost weight, became apathetic and acquired a staring, idiotic facial expression. Laughing and crying occurred spontaneously in turns, the motions of the

extremities acquired a marionette-like character, and death followed as a result of marasmus or intercurrent diseases, chiefly bronchopneumonia. Atrophy of the optic nerve and bluish white discoloration of the macula with a cherry red spot in the fovea were observed in each patient. Histologically, there were observed edema of the retina, preferably of the external layers; edema or exudations between the rods and the cones toward the pigment layer and lamina; distention; formation of vacuoles; degeneration and atrophy of the amacrine cells and absence of Nissl bodies. Werncke points out some differences in his findings from those of other writers and a phenomenon, not previously described, namely, a dark spot on the temporal side of the fovea, observed under transillumination. According to Werncke, who accepts Leber's explanation, this dark spot is caused by edema. The genesis of this spot is discussed in detail. K. L. STOLL. [ARCH. OPHTH.]

FOLLOW-UP STUDY OF PSYCHOPATHIC CHILDREN. P. A. SCHWALBE-HANSEN, Hospitalstid. **81**:407 (April 26) 1938.

Of 98 children suffering from psychopathic symptoms of different kinds and genesis who were observed and treated at a psychiatric clinic in the period from 1920 to 1932, 77 were reexamined in 1937.

| | | Classification in 1937 | | | |
|---|---|---|---|---|---|
| Original Classification | Patients | Healthy | Psycho-pathic | Psychically Debilitated | Psychotic |
| Reactions against environment.... | 33 | 20 | 3 | 2 | .. |
| Pubertal crisis ..... | 11 | 5 | 4 | .. | .. |
| Hypervitality ..... | 13 | 6 | 3 | .. | 1 |
| Psychopathy ..... | 25 | 5 | 13 | .. | 1 |
| Mental debility ..... | 13 | 2 | (8) | 8 | .. |
| Postencephalitic syndrome ..... | 3 | 1 | .. | 2 | .. |

WALLGREN, Göteborg, Sweden.

## Diseases of the Genitourinary Tract

TREATMENT OF GONORRHEAL VAGINITIS WITH CORBUS-FERRY GONOCOCCUS FILTRATE. L. E. GOLDBERG and K. BLANCHARD, J. Pediat. **13**:381 (Sept.) 1938.

Twenty-four girls ranging in age from 2 to 10 years were treated for gonorrheal vaginitis with intracutaneous injections of Corbus-Ferry gonococcus filtrate. The doses of the gonococcus filtrate ranged from 0.0083 cc. initially to 0.01 and 0.2 cc., given biweekly. In 15 of the patients the condition was acute and in 9 chronic. Eighteen patients were considered cured, but 5 of these subsequently had recurrences. The duration of treatment resulting in cure ranged from twenty-eight to one hundred and sixty-five days, with an average length of treatment of seventy-three and forty-four hundredths days. Thirteen, or 54.17 per cent, of the 24 patients have had no recurrence. The length of time after dismissal from the hospital without a recurrence has varied from one hundred and eighty to five hundred and eight days. Six patients (25.0 per cent) not cured were treated over a period ranging from ninety-three to one hundred and sixty-five days without apparent improvement. No difference in results of treatment was apparent between chronic and acute vaginitis.

RAUH, Cincinnati.

SURGICAL SIGNIFICANCE OF URINARY INCONTINENCE IN INFANTS AND CHILDREN. T. H. LANMAN and J. H. MOORE, New England J. Med. **219**:777 (Nov. 17) 1938.

Lanman and Moore report in detail, with illustrations, on 6 children showing interesting abnormalities of the urinary functions, namely: (1) a boy of 2½ years

with posterior urethral valves; (2) a girl of 3 weeks with congenital cyst of the vagina; (3) a boy of 2½ years with rhabdomyosarcoma of the bladder; (4) a girl of 2½ years with lipoma of the spinal canal; (5) a girl of 8 years with vesicovaginal fistulas caused by insertion of a hairpin at 3 years, and (6) a girl of 9 years with ectopic ureter, who had a double kidney with a double pelvis on the left and a single ureter. This patient had been operated on shortly after birth for an imperforate anus.

GENGENBACH, Denver.

ABNORMALITIES OF THE URINARY TRACT IN "ESSENTIAL HYPERTENSION." H. A. SCHROEDER and J. M. STEELE, Proc. Soc. Exper. Biol. & Med. **39**:107 (Oct.) 1938.

Abnormalities of the urinary tract are frequently present in young persons suffering from "essential hypertension," as was demonstrated in pyelograms obtained after intravenous injection of diodrast. In 50 of 71 patients some abnormality was present. Under these circumstances it seems desirable to explore further the meaning of these phenomena.

HANSEN, Minneapolis.

A CASE OF RENAL DWARFISM WITH POLYURIA, POLYDIPSIA AND EXOPHTHALMOS. P. LEREBOULLET, M. LELONG and J. BERNARD, Bull. Soc. pédiat. de Paris **36**: 378 (June) 1938.

A boy 11½ years old weighed 22.6 Kg. and measured 1.24 meters in height. He had polydipsia. His head was long and flattened above, and exophthalmos was present. Renal function tests showed marked insufficiency. The blood urea was persistently elevated, and the blood pressure rose gradually under observation. The carbon dioxide–combining power of the plasma was 34, indicating marked acidosis. Roentgen examination of the bones, including the skull, gave negative results. On account of the marked impairment of renal function, pyelography was not performed.

BENJAMIN, Montreal, Canada.

RENAL INSUFFICIENCY AND A LESION OF THE VESICAL NECK IN A YOUTH. H. ROUÈCHE and J. SABOURIN, Bull. Soc. pédiat. de Paris **36**:626 (Oct.) 1938.

A youth 18 years old had marked renal insufficiency. This did not improve appreciably over a period of six months after medical and surgical treatment. The latter consisted of electrocoagulation for hypertrophy of the neck of the bladder.

BENJAMIN, Montreal.

CAUSES AND TREATMENT OF ENURESIS IN CHILDHOOD. F. G. VON STOCKERT, Med. Klin. **34**:1156 (Sept. 2) 1938.

Von Stockert elaborates on the various causes and treatments of enuresis in children. He regards enuresis as a neurosis or a functional disturbance and recommends treatment on a psychologic basis. The child must be reassured that the condition is avoidable and can be discontinued at any time. Treatment should be begun before the child has accepted his affliction as inevitable and has arranged (narrowed) his life and associations accordingly.

SIEMSEN, Chicago.

RENAL TUBERCULOSIS IN CHILDREN. C. SATOMI, Acta pædiat. japon. **45**:276 (Feb.) 1939.

Satomi reports tuberculosis of the kidney in 2 children, the first an infant of 1 year and 8 months and the second a child 6 years old. The prominent symptoms were pyuria, tuberculous bacilluria, pain on urination and pyelographic findings. Emphasis is placed on the fact that clinical renal tuberculosis must be distinguished from anatomic tuberculosis of the kidneys, often seen in tuberculous patients.

KATO, Chicago.

## Diseases of the Ductless Glands; Endocrinology

EFFECT OF FAT ON THE RATE OF AVAILABILITY OF ORALLY INGESTED CARBOHYDRATE. H. POLLACK and H. DOLGER, Proc. Soc. Exper. Biol. & Med. **39**:239 (Nov.) 1938.

Pollack and Dolger previously had shown that the ingestion of rapidly available carbohydrates by diabetic patients using protamine zinc insulin resulted in rapid rises and precipitous drops in the concentration of sugar in the blood which undoubtedly were responsible for the difficulties encountered in the clinical management of these patients (*Proc. Soc. Exper. Biol. & Med.* **38**:577, 1938). Twenty-five patients with severe diabetes maintained on protamine zinc insulin exclusively were given 220 Gm. of banana twenty-four hours after the insulin, and the blood sugar was determined every half hour for four hours. After ten days this was repeated, and 4 ounces (124.5 Gm.) of 30 per cent cream was also given. All patients responded in the same way: There was a delay in the maximum absorption from one to two hours, and the precipitous drops in blood sugar were eliminated. This sustained absorption seen with the fat mixtures tended to prevent the disturbing posthyperglycemic hypoglycemia in these patients, management of whom was difficult.

HANSEN, Minneapolis.

PROTEIN AS A SOURCE OF CARBOHYDRATE FOR PATIENTS USING PROTAMINE ZINC INSULIN. H. POLLACK and H. DOLGER, Proc. Soc. Exper. Biol. & Med. **39**:242 (Nov.) 1938.

J. W. Conn and L. H. Newburgh (*J. Clin. Investigation* **15**:665, 1936) recommended diets high in protein in the treatment of patients for spontaneous hypoglycemia. Forty diabetic patients were given 400 Gm. of lean chopped beef twenty-four hours after the injection of protamine zinc insulin. The blood sugar was determined at one-half hour intervals for four hours. Uniformly there was a slow but definite rise and no precipitous drop in the blood sugar. Application of this principle to the problem of the effect of protamine zinc insulin has eliminated nocturnal hypoglycemia. Patients are instructed to take 50 per cent or more of the daily allowance of protein at the evening meal.

HANSEN, Minneapolis.

EFFECT OF LOCAL APPLICATION OF TESTOSTERONE IN AN OINTMENT ON GROWTH OF PENIS IN THE RAT. R. R. GREENE and H. S. WIGODSKY, Proc. Soc. Exper. Biol. & Med. **39**:307 (Nov.) 1938.

Twenty-four day old albino rats were used to determine the effect of local applications of testosterone (0.075 mg. daily) to the penis. The animals were killed after twenty-three days of treatment. The penis was dissected from the prepuce and surrounding tissue, measured and weighed. Among castrate rats the growth of the penis was approximately the same in the animal treated locally as in the untreated control and in the animal given subcutaneous injections of the same amount of testosterone. The growth of the prostatic–seminal vesicle complex was the same in the locally treated rat as in the rat given the material subcutaneously. As measured by gross testicular weight, the growth of testes was not appreciably inhibited by local applications of testosterone to the penis in the doses used in this experiment (75 micrograms per day for twenty-two days).

HANSEN, Minneapolis.

MECHANISM OF INSULIN CONVULSIONS: I. SERUM ELECTROLYTES AND BLOOD SUGAR IN RELATION TO OCCURRENCES OF CONVULSIONS. M. ZIEGLER and I. MCQUARRIE, Proc. Soc. Exper. Biol. & Med. **39**:523 (Dec.) 1938.

This investigation was undertaken to determine whether or not there is any relation between the decrease in potassium and inorganic phosphorus and the

occurrence of convulsions after the administration of insulin in convulsive doses. Eighty experiments on the effects of insulin alone were carried out on 43 fasting dogs. In contrast with the findings in relation to the hypoglycemic curve, there was no evidence of a tendency for convulsions to occur at the lowest point on either the serum potassium or the serum phosphorus curve. Typical convulsions could be induced even when the levels of serum phosphorus and potassium were maintained within a normal range by continuous administration of phosphorus and potassium salts. Administration of sodium salts had no definite effect on the occurrence of seizures.

HANSEN, Minneapolis.

MECHANISM OF INSULIN CONVULSIONS: II. EFFECTS OF VARYING PARTIAL PRESSURES OF ATMOSPHERIC $O_2$, $N_2$ AND $CO_2$. I. McQUARRIE and M. R. ZIEGLER, Proc. Soc. Exper. Biol. & Med. **39**:525 (Dec.) 1938.

The primary purpose of the experiments reported was to determine the effects of breathing atmospheres varying greatly in their partial pressures of oxygen ($O_2$), nitrogen ($N_2$) and carbon dioxide ($CO_2$) on the occurrence of convulsions following the administration of insulin. High carbon dioxide (15 per cent) or low oxygen (5 to 9 per cent) pressure or the two conditions combined definitely tended to prevent or greatly delay insulin-induced convulsions even when the blood sugar was reduced to the convulsive level established for each dog during a preliminary test in room air. High oxygen (60 to 76 per cent) or low carbon dioxide (5 to 9 per cent) pressure had little or no influence on the occurrence of convulsions.

HANSEN, Minneapolis.

MYXEDEMA AND GENERALIZED MUSCULAR HYPERTROPHY. DENOYELLE, DE GRAILLY and SIRAND, Bull. Soc. pédiat. de Paris **36**:590 (Oct.) 1938.

A boy 3 years old showed generalized muscular hypertrophy and hypertonicity, signs of thyroid deficiency and mental retardation, all of which improved after he was given thyroid extract by mouth.

BENJAMIN, Montreal.

A CASE OF THE LAURENCE-MOON-BIEDL SYNDROME. T. OHTA and T. HASEBE, Acta pædiat. japon. **45**:53 (Jan.) 1939.

The occurrence of the Laurence-Moon-Biedl syndrome in a girl 10 years old is reported. The five classic manifestations of this syndrome were all present, namely, (1) obesity, (2) retinal changes, (3) mental retardation, (4) supernumerary fingers and (5) sexual infantilism.

KATO, Chicago.

DIABETIC CHILDREN ON FREE DIET. K. BOJLÉN, Nord. med. tidskr. **15**:714 (April 30) 1938.

Bojlén reports that 16 diabetic children were treated successfully with ordinary insulin given in one or two injections daily, without any dietetic restrictions.

WALLGREN, Göteborg, Sweden.

DIETETIC TREATMENT OF DIABETIC CHILDREN. V. CLAUSEN, Nord. med. tidskr. **15**:716 (April 30) 1938.

At the pediatric clinic of Copenhagen diabetic children are given a diet which is balanced according to the habits and needs of the child, with a fixed maximum caloric value per day and with most of the carbohydrates given during the first half of the day. Protamine insulin is used, one injection being given each day, in the evening. The children are examined every month as a routine and, in addition, whenever they show morbid symptoms. The mothers of the children examine the urine every second day with iron chloride. The so-called free diet is criticized and the risk of adiposity and of increased frequency of cardiosclerosis in adult life is discussed.

WALLGREN, Göteborg, Sweden.

So-Called Free Diet in the Treatment of Diabetic Children. A. Wallgren, Svenska läk.-tidning **35**:622 (April 22) 1938.

The term "free diet" is an unfortunate one, as no child, even a healthy one, should eat what it likes. It is absolutely unnecessary that diabetic children eat candies and other forms of sweets, and their diet ought under all circumstances to be free from these. The diabetic child should receive a diet that is as similar as possible to that of a normal child. In this way any possible psychic depression produced by a restricted diet is eliminated, and the mother's job in the kitchen is much easier, as she need not prepare special dishes for her diabetic child, all the members of the family eating the same food. With such a "modified normal diet" and protamine insulin diabetic children are kept in good condition with less risk of acidosis. It is necessary, however to supervise them regularly. No acetonuria and no polyuria should be tolerated, and if either appears, the dose of insulin must be increased, and eventually the diet must be changed in some way.

Wallgren, Göteborg, Sweden.

Urinary Excretion of Androgen During Treatment for Adiposogenital Dystrophy. K. Sand and P. Plum, Ugesk. f. læger **100**:719 (June 30) 1938.

Of 3 boys treated for adiposogenital dystrophy with a gonadotropic substance and thyroidin (an extract of sheep thyroids), an increased excretion of androgen was demonstrable in 2. At the same time a distinct clinical amelioration was noted.

Wallgren, Göteborg, Sweden.

## Diseases of the Muscles, Bones, Joints and Lymph Glands

Maggot Therapy for Hematogenous Osteomyelitis of the Tibia. S. Maddock and D. Jensen, Arch. Surg. **37**:811 (Nov.) 1938.

The report deals with 29 cases in which hematogenous osteomyelitis of the tibia was treated with maggots. Of 31 lesions in 29 patients, 26 were closed, 1 still required treatment, 2 had necessitated amputation and 2 were fatal. The maggot treatment is described in detail, the objections and the advantages being brought out. The authors feel that the advantages of maggot therapy for osteomyelitis outweigh the objections and that this form of treatment is not a medical fad but a significant contribution to science.

Kaiser, Rochester, N. Y.

"Mirror Twins" and Double Center of Ossification for the Semilunar Bone. R. Turpin, M. Tisserand and J. Piton, Bull. Soc. pédiat. de Paris **36**:390 (June) 1938.

Monozygotic male twins were identical in some respects but slightly dissimilar in others. Roentgen examination of their wrists revealed double centers of ossification for the semilunar bones, more advanced in one than in the other boy. One of the twins had a dermoid cyst which had become infected, producing an anal fistula which required surgical intervention.

Benjamin, Montreal, Canada.

A Case of Severe Osteopsathyrosis with Hypercalcemia. M. Kaplan, Bull. Soc. pédiat. de Paris **36**:396 (June) 1938.

A boy 17 years old had a number of deformities as a result of multiple fractures. No other members of the family had a like condition. His scleras were not blue, and he was not deaf. His blood showed 12.9 mg. of calcium per hundred cubic centimeters, 5.5 mg. of phosphorus and a normal amount of phosphatase. There was a high output of calcium in the urine.

Benjamin, Montreal, Canada.

GENESIS OF PROGRESSIVE MUSCULAR DYSTROPHY WITH PARTICULAR REFERENCE TO THE PANCREAS. M. ANTONINI and G. SEMPRINI, Med. inf. **9**:293 (Oct.); 353 (Dec.) 1938.

Progressive muscular dystrophy has been ascribed to many factors, both exogenous and endogenous. The exogenous factors are: (*a*) trauma and physical defect, (*b*) toxic substances (alcohol, mercury, lead), (*c*) infections (fetal infection, syphilis, tuberculosis), (*d*) rheumatic conditions, (*e*) consanguinity. The endogenous factors may be grouped into the following classes: (*a*) the muscular, (*b*) the nervous, (*c*) the hereditary degenerative, (*d*) the biochemical and metabolic and (*e*) the endocrine. The literature covering each of the five endogenous groups is discussed.

Eight cases of progressive muscular dystrophy are reported. In each the carbohydrate metabolism was studied by examination of ferments obtained from the duodenum and by studies of blood sugar curves following ingestion of sugar and injection of epinephrine hydrochloride. The data obtained did not reveal any correlation between the secretions of the pancreas and progressive muscular dystrophy.

HIGGINS, Boston.

A CASE OF MULTIPLE PERIOSTITIS. G. MUHL, Nord. med. tidskr. **15**:583 (April 15) 1938.

A breast-fed girl of 6 weeks, previously healthy with the exception of diarrhea for a short period at the age of 1 month, was found to have a slightly painful swelling of the left tibia. Roentgenographically, periostitic changes were demonstrated on the long bones of all extremities and on the mandible. The Wassermann and tuberculin tests were negative. There was no fever. The sedimentation rate was normal. There was no leukocytosis. Three months later roentgen examination showed normal conditions. The periositis is considered to have been of infectious origin, probably produced in connection with the enteritis.

WALLGREN, Göteborg, Sweden.

OSSEOUS XANTHOMATOSIS. G. A. LANDOFF, Nord. med. tidskr. **16**:2036 (Dec. 24) 1938.

The patient was a boy of 16 years of a healthy family. Spontaneous fractures had been occurring since he was 6 years of age, causing deformities. He was first seen in November 1936, when he was 15 years old. He had multiple large café au lait pigmented areas in the skin (histologically there was no xanthomatosis). Puberty was retarded. Invalidizing deformities had been caused by the multiple fractures. Roentgenograms of the skeleton disclosed multiple areas of decalcification in the skull, hands, feet and long bones. The sella turcica was slightly diminished in size. The blood calcium was 11.2 to 11.7 mg. per hundred cubic centimeters. The blood cholesterol was 186 to 228 mg. per hundred cubic centimeters. There was no polyuria, and there were no morphologic changes of the blood except eosinophilia of 9 to 10 per cent. The sedimentation test was 5 mm. The basal metabolic rate was +30 to +42 per cent. There was no adenoma of the parathyroids (exploratory operation). Histologic examination showed typical xanthomatous cells with foam cytoplasm and a small nucleus. The ratio of cholesterol to cholesterol ester in the osseous matter was 4.4:1; normally the ratio is 1:2. In Hand-Schüller-Christian disease the relation is 1:5. The patient was treated with roentgen rays, perhaps with some success. He was observed for two years.

WALLGREN, Göteborg, Sweden.

EWING'S SARCOMA. V. H. FANÖE, Ugesk. f. læger **100**:1185 (Oct. 20) 1938.

A boy of 9 was admitted to the hospital as having rheumatic fever. Three months previously he had suffered a trauma against his left elbow, with consecutive pain, swelling and fever. After some time similar symptoms and signs

developed in the right arm. Shortly before admittance to the hospital there occurred a swelling of the right side of the chin. A roentgenogram displayed a cystic tumor of the right maxilla. A new attack of pains in the joint of the left arm occurred, and roentgen findings indicated involvement of the left radial bone, sarcoma suspected. The maxillary tumor was operated on. Microscopically it proved to be Ewing's sarcoma. There was temporary amelioration after radiologic treatment. A tendency to metastasize was noted.

WALLGREN, Göteborg, Sweden.

SPONTANEOUS GENERAL OSTEOPOROSIS IN A SMALL GIRL. J. C. SCHIPPERS, Maandschr. v. kindergeneesk. **8**:108 (Nov.) 1938.

A girl was healthy till the age of 8 years and then complained of pains in the legs. The pains were followed by a fracture, which on roentgen examination appeared to be caused by general osteoporosis. The administration of calcium and vitamin D resulted in complete recovery. Referring to the literature and regarding the favorable results of the therapy, Schippers assumes the cause of the osteoporosis to have been a deficiency disease.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of the Eye

SULFANILAMIDE IN THE TREATMENT OF GONORRHEAL OPHTHALMIA IN CHILDREN. M. W. MICHELS, J. Pediat. **13**:527 (Oct.) 1938.

Fifteen children with gonorrheal ophthalmia were treated with sulfanilamide. The ages ranged from 5 days to 3 years. The results obtained were compared with those obtained in children treated over a two year period prior to the use of sulfanilamide. The most satisfactory observation in connection with the use of sulfanilamide was the rapid decrease in the swelling and discharge. Patients with red, chemotic bulbar conjunctivae, swollen retrotarsal folds and tumefied lids showed uniformly prompt subsidence. This type of condition is more apt to progress to corneal involvement if untreated, and the rapid arrest of these symptoms with sulfanilamide is responsible for protection against complications and a much better prognosis. A reduction of hospitalization of from twenty-eight and one-half days for the control series of 32 patients to five and eight-tenths days for the 15 patients treated with sulfanilamide is of economic importance.

RAUH, Cincinnati.

FURTHER STUDIES ON THE REGENERATION OF THE AQUEOUS IN MAN. P. C. KRONFELD and C. K. LIN, Proc. Soc. Exper. Biol. & Med. **39**:259 (Nov.) 1938.

A fine hypodermic needle was introduced into the anterior chamber of the human eye and the aqueous entirely removed. One hour after the fluid was obtained, it was found by another puncture that regeneration of aqueous takes place at the same absolute rate in all eyes. Intraocular tension was also followed, and the extent of regeneration of the aqueous depended on the original volume of the chamber. In this investigation the amount of fluid regenerated in thirty minutes was studied in fairly normal eyes with use of a 23 gage needle and local anesthesia induced with 1 per cent pontocaine hydrochloride. The amount of fluid regenerated in thirty minutes after complete removal of the aqueous tended to be greater in those eyes with the larger initial volume. In none of the 12 human subjects studied did any lasting untoward effects occur as regards either function or appearance of the eye. Some of those with retrobulbar neuritis or optic atrophy experienced temporary or lasting improvement of vision after puncture of the anterior chamber.

HANSEN, Minneapolis.

## Skin Diseases; Allergy

SOME OBSERVATIONS ON THE BLOOD EOSINOPHIL COUNT IN ASTHMATICS. H. B. HUNT, J. Allergy **10**:146 (Jan.) 1939.

Hunt seeks to explain the divergences which occur in the eosinophil counts of allergic patients. Counts were done on the blood of 103 asthmatic patients; on 27 patients serial counts were done in each of four quarters of the year; on 9 the counts were done in each of three quarters of the year.

The eosinophil count is subject to large fluctuations, the cause of which is not ascertainable. The count in bronchial asthma is usually around 5 per cent. It is difficult to differentiate between intrinsic and extrinsic or between infective and noninfective forms on the basis of eosinophil counts. There is no suitable explanation for the seasonal variation of the count, i. e., the tendency for the count to be higher in the summer months.

HOYER, Cincinnati.

ORAL ADMINISTRATION OF RAGWEED POLLEN. J. H. BLACK, J. Allergy **10**:156 (Jan.) 1939.

Black has treated hay fever by oral therapy for a number of years in a gradually decreasing number of patients. He tried it again on 40 patients during the ragweed season of 1938. He concluded: "Oral therapy with ragweed pollen gives perfectly satisfactory results in a larger group, but does not compare favorably with the results obtained by hypodermic treatment. In three patients it was found that the oral administration of pollen made it possible to increase the hypodermic treatment much more rapidly than could be done before pollen was administered by mouth.

HOYER, Cincinnati.

THE NERVOUS SYSTEM IN ACRODYNIA: REVIEW OF THE LITERATURE AND REPORT OF A CASE. A. J. LUBIN and H. K. FABER, J. Pediat. **13**:515 (Oct.) 1938.

A review of the literature discloses pathologic changes in the central nervous system in acrodynia which are not constant in occurrence, kind or localization and which do not offer a satisfactory explanation of the clinical picture. A case of acrodynia is reported with the observations at autopsy. Degenerative changes were found in the cells of the anterior horn of the lumbosacral region and in the intermediolateral cell column of the spinal cord. No pathologic changes were found in serial sections through the diencephalic sympathetic nuclei. This observation fails to support the belief that this region is the primary focus of involvement.

RAUH, Cincinnati.

SUBACUTE INFECTIOUS EDEMA IN INFANTS. R. DEBRÉ, J. MILHIT, M. LAMY, A. HANAUT and S. KAPLAN, Bull. Soc. pédiat. de Paris **36**:611 (Oct.) 1938.

Protracted infection of the respiratory tract in 2 very young infants is reported. The characteristic finding was subacute pulmonary edema. One child recovered, and the other died. Necropsy revealed diffuse bronchopneumonia in the latter. The characteristic roentgenogram of the chest in this condition shows diffuse tiny nodular infiltrations and broad intercostal spaces. The prognosis is said to be fairly good.

BENJAMIN, Montreal.

A STATISTICAL CONTRIBUTION ON THE GENESIS OF SERUM SICKNESS. F. SCHMIDT, Časop. lék. česk. **76**:77 (Jan. 22) 1937.

Of 1,047 patients given serum therapy, 121 had a history of previous injections of foreign serum, and 36, or 29.75 per cent, of these had a serum reaction. Of the 926 with apparently no previous injections of serum, 108, or 11.66 per cent, had a reaction. There was 1 death (0.7 per cent), which occurred two and one-half hours after injection of the serum in a child with membranous tonsillitis and,

at autopsy, acute myocarditis. There were 9 (6.2 per cent) severe reactions, with collapse, vomiting, severe urticaria and generalized pains, 37 (25.7 per cent) moderate reactions, with urticaria and rheumatoid pains, and 97 (67.3 per cent) mild reactions, with mild urticarial symptoms. The reaction seems to be related to individual susceptibility and to the type of animal supplying the serum, but the latter factor was not studied since no record was made of the animal donors. The number of apparently primary recipients who had a reaction is surprising. A second injection increased the morbidity of the reaction two and one-half times, but with precautions this danger was minimized.

STULIK, Chicago.

FEER'S DISEASE IN JAPAN. Y. HIRO, S. TASAKA and K. TAKAHASHI, Acta pædiat. japon. **44**:1885 (Dec.) 1938.

Acrodynia in a 1½ year old girl is reported. The duration of the disease was approximately two months, and a satisfactory recovery was noted under calcium and atropine medication. Eight other cases observed in Japan are reviewed.

KATO, Chicago.

INTRACRANIAL MANIFESTATIONS OF RECKLINGHAUSEN'S DISEASE. T. DALSGAARD-NIELSEN, Hospitalstid. **81**:661 (June 28) 1938.

1. A boy of 12 years had always had strabismus, impaired vision in the right eye and scattered pigmented areas and soft flat bean-sized nodules in the skin. Some months later the right eye had become totally blind, and vision in the left eye was becoming impaired. Examination revealed atrophy of the right optic nerve and temporal hemianopia and papillitis of the left eye. In roentgenograms an involvement of the sella turcica and of the optic foramens was demonstrated. At operation an encapsulated astroblastoma, starting from the bottom of the third ventricle, was found.

2. A girl of 7 on examination at school was found to have impaired sight. She had scattered café au lait spots, numerous pigmentations and some fibromas of the skin. Vision in the right eye was 6/60; there was perception of light with the left eye; both papillae were atrophic; the visual fields were somewhat diminished; there was paresis of the abducens nerve, also exophthalmos, on the left side. Roentgenologically there was enlargement of both optic foramens. At operation an intrachiasmatic tumor (oligodendrocytoma) involving both optic nerves was extirpated. The impairment of sight was ameliorated after this operation.

3. The patient was a girl of 7. The mother had pigmentations and nodules in the skin. Since birth the girl had shown pigmented spots and larger pigmented areas. During the last three years her sight had gradually become impaired. Vision was 6/60 in both eyes. There was atrophy of the papillae as well as restriction of the visual fields. Roentgenograms showed enlargement of the optic foramen. At operation an intrachiasmatic gliomatous tumor of the same type as that in the last-mentioned case, involving the optic nerves, was partially extirpated.

WALLGREN, Göteborg, Sweden.

TWO CASES OF EPIDERMOLYSIS BULLOSA HEREDITARIA DYSTROPHICA. S. W. ERICHSEN, Norsk mag. f. lægevidensk. **99**:185 (Feb.) 1938.

Two children, brother and sister, 12 and 7 years of age, had suffered from bullous efflorescences predominantly in traumatically exposed areas of the skin, besides changes of the nails. The disease began when the children were about 9 months old. The father and his sister and brother displayed dystrophy of their nails but no cutaneous manifestations of the disease.

WALLGREN, Göteborg, Sweden.

A Family with Multiple Neurofibromatosis (Recklinghausen). F. Harbitz, Norsk mag. f. lægevidensk. **99**:609 (June) 1938.

Harbitz reports multiple neurofibromatosis or extensive pigmentation of the skin occurring in three generations of a Norwegian family. In the last generation all of the 9 children suffered from the disease. The youngest ones, girls of 14½, 12½ and 10 years, displayed only multiple pigmented spots.

Wallgren, Göteborg, Sweden.

Ovalbumin Test in Infantile Eczema. G. Gezelius, Svenska läk.-tidning. **35**:484 (April 1) 1938.

Of 50 infants with atopic eczema tested percutaneously with fresh ovalbumin, 24 showed a positive reaction. This test evoked no positive reaction in infants with seborrheic dermatitis.

Wallgren, Göteborg, Sweden.

A Case of Annular Erythema. D. H. Nathorst, Svenska läk.-tidning. **35**: 2091 (Dec. 16) 1938.

A boy of 14 years who suffered from somewhat obscure pains in his joints and who had a rapid erythrocytic sedimentation rate but no demonstrable involvement of the heart displayed an eruption of annular erythema, proving the rheumatic cause of the symptoms.

Wallgren, Göteborg, Sweden.

Scleroderma in Bands and Parathyroidectomy. W. Naessens, Maandschr. v. kindergeneesk. **8**:173 (Feb.) 1939.

Naessens gives a description of extensive and progressive scleroderma in bands in a girl of 11 years. Extirpation of a parathyroid gland resulted in amelioration, which lasted for about nine months. The author is of the opinion that the sclerodermic syndrome does not have its cause wholly in the parathyroids. Parathyroidectomy may explain why the calcium has returned from the calcified skin to the decalcified skeleton.

van Creveld, Amsterdam, Netherlands.

Dermatorrhexis with Dermatochalasis and Arthrochalasis (Danlos-Ehlers Syndrome). J. Van Aardenne, Maandschr. v. kindergeneesk. **8**:187 (Feb.) 1939.

A boy of 9 years showed the Danlos-Ehlers syndrome. There was extraordinary vulnerability of the skin and its blood vessels; the skin was very elastic, and the joints were hyperextensible and hyperflexible.

van Creveld, Amsterdam, Netherlands.

## Teeth and Dentistry

Influence of Metabolism on Teeth. J. O. McCall and F. Krasnow, J. Pediat. **13**:498 (Oct.) 1938.

Metabolic factors are considered to have much to do with the cause and control of dental caries. They may influence the incidence of caries in one of two ways: (1) The tooth structure may be defective (shown chiefly as hypoplasia of the enamel) because of abnormal metabolism during the period of the formation of the tooth, making it susceptible to what may be called amelolytic influences; (2) current metabolic influences may be at work, expressing themselves as functions of the saliva, which controls largely the environment of the tooth, and possibly through nutrient channels within the tooth. Quantitative analyses of the saliva of persons suffering from caries or erosion and of persons who are caries free indicate that in the presence of erosion the average range of the concentration of hydrogen ion, calcium, magnesium, inorganic phosphate, protein, lipid phos-

phorus and cholesterol lies entirely beyond that of the same constituents in the saliva of normal persons. In persons with active caries variations from the normal were found to be fewer, nonoverlapping figures appearing only for the concentration of hydrogen ion, magnesium, lipid phosphorus and cholesterol. The results imply a tendency toward that type of derangement often associated with acidic states in the body. The authors believe that the variations noted in the saliva in different oral conditions indicate that the condition of the teeth is associated not with calcium metabolism alone but with several specific metabolisms on which the general metabolism depends and that dental health is closely related to the health and life of the body as a whole. A case is presented in which aberrant salivary values were brought within normal range by nutritional regulation.

RAUH, Cincinnati.

DIET AND DENTAL CARIES. R. W. BUNTING, New York State J. Med. **39**:18 (Jan. 1) 1939.

The active destructive agent in dental caries is some form of organic acid formed on the tooth by products of the local fermentation of carbohydrates. The most prominent of bacterial agents is the oral Lactobacillus acidophilus. While lack of cleanliness may produce caries, it is not the most important cause. Caries is not associated with either a low calcium or a low phosphorus intake. Forcing of viosterol, calcium and phosphorus, and vitamin C fails to reduce caries. The most important etiologic factor is acid-producing bacteria, and the most effective method of reducing dental caries is to eliminate sugar and starch from the diet. In Michigan a clinic for the control of caries is now in operation, where bacterial counts of oral L. acidophilus are made on samples of saliva sent to the laboratory.

AIKMAN, Rochester, N. Y.

## Miscellaneous

SULFAPYRIDINE. P. H. LANG, J. A. M. A. **112**:538 (Feb. 11) 1939.

In a preliminary report of the Council on Pharmacy and Chemistry, Lang voices its present opinion on the therapeutic status of sulfapyridine (2-[para-aminobenzenesulfonamido]-pyradine), indicating that, as a result of the work of Whitby and others abroad and that reported here, its use may be tried in pneumococcic, severe staphylococcic and Friedländer's bacillus infections. In hemolytic streptococcic, meningococcic, gonococcic or Welch bacillus infections its use is not as yet warranted to supplant sulfanilamide. Reactions are as severe and frequent as with sulfanilamide. Agranulocytosis is a possible reaction. In view of the work presented, and since a rational program of treatment has not been presented, it is advised that at present general use of sulfapyridine is not warranted.

HEERSMA, Kalamazoo, Mich.

UNEXPECTED DEATH IN EARLY LIFE. S. FARBER, New England J. Med. **219**:836 (Nov. 24) 1938.

The subject is discussed as viewed by a pathologist from the standpoint of many interesting autopsies. Included in the survey are cases of death due to congenital anomaly, cases of unexpected termination of known diseases in the neonatal period and cases of death in infants and children previously in good health.

GEGENBACH, Denver.

EFFECT OF SORBITOL AND SUCROSE ON CEREBROSPINAL FLUID PRESSURE AND URINE OUTPUT. H. G. SCHWARTZ and R. ELMAN, Proc. Soc. Exper. Biol. & Med. **39**:506 (Dec.) 1938.

Parallel experiments were run on 9 pairs of dogs in a comparison of the relative merits of sucrose and sorbitol as agents for reducing the pressure of cerebro-

spinal fluid and effecting diuresis. Under pentobarbital sodium anesthesia, 50 per cent sucrose and 50 per cent sorbitol were given intravenously in a dose of 2.5 cc. of a 50 per cent solution per kilogram at the rate of 7 cc. per minute. A more rapid rate of injection caused an initial rise in the pressure of the cerebrospinal fluid. Sorbitol reduced the pressure to a definitely greater degree and for over twice as long an interval as sucrose, and very little secondary rise occurred after the administration of sorbitol. The diuresis following the injection of sorbitol was also definitely greater. Thus, sorbitol is more efficient in reducing the pressure of cerebrospinal fluid and has a greater diuretic effect than sucrose when given in equivalent doses.

HANSEN, Minneapolis.

HISTOLOGIC DIAGNOSIS OF EMBRYONAL LIPOMA. G. GRICOUROFF, Bull. Assoc. franç. p. l'étude du cancer **27**:251, 1938.

An encapsulated tumor with a tendency to recur and occasionally even to metastasize which originates wherever adipose tissue is present but is seen most frequently in the thigh and in the retroperitoneal space can be easily mistaken for myxoma unless frozen sections are stained for fat, for it resembles myxoma closely in the gross and even microscopically. Droplets varying in size from very small ones to such large ones as to fill the entire cell are found; they are more numerous away from the blood vessels. Mucicarmine staining shows the characteristic color reaction in the interstitial tissue but never in the protoplasmic droplets. That finding is, according to Masson, pathognomonic for true myxoma. The fat droplets in embryonal lipoma or, as it is sometimes called, myxomatous lipoma are not due to degenerative changes in the nuclei. They are a product of cellular secretion and are pathognomonic for the lipoma. It may be necessary to consider: 1. A myxoma that invades fat tissue. In that case there will be compact lobules of adult adipose tissue, but there will be no fat droplets in the young tumor cells. 2. An undifferentiated sarcoma with fatty degeneration. In that case other signs of degeneration and of necrosis will be found. 3. Xanthogranuloma. The spongiocytes (foam cells) characteristic of the latter will help to make the correct diagnosis. Some authors claim that embryonal lipoma is essentially benign and that the recurrences and metastases are evidences of a multicentric, systemic nature of growth.

I. DAVIDSOHN. [ARCH. PATH.]

ALCOHOLIC COMA IN CHILDREN. R. DEBRÉ, M. LAMY and S. KAPLAN, Bull. Soc. pédiat. de Paris **36**:605 (Oct.) 1938.

A boy 4 years old and a girl 9 years old showed acute alcoholic poisoning after ingestion of wine. There was a short period of excitement, which was followed by deep coma. They recovered. A lethal dose of absolute alcohol is estimated as being between 6 and 7 cc. per kilogram of body weight. In the cases reported the intake was much less if one may assume that the alcoholic content of the wine was 8 per cent.

BENJAMIN, Montreal.

CARBON MONOXIDE POISONING OF A CHILD. B. WOLLEK, Orvosi hetil. **82**:974 (Oct. 1) 1938.

A 12 year old child went into a room which was heated with charcoal. Thirty minutes later he was found there unconscious. He regained consciousness two hours later. The child seemed to recover and was able even to go to school. On the morning of the sixth day he awakened with a bad headache and did not see anything. Examination of the eyes did not show any objective pathologic changes. Neurologic examination showed a normal neurologic condition. The blood contained carbon monoxide, which could be demonstrated for as long as fourteen days. The child regained his sight in three days.

GÖTTCHE, Budapest, Hungary.

THE CONSTITUTION. T. BRANDER, Finska läk.-sällsk. handl. **81**:352 (April) 1938.

The constitution is an expression of the individual's ability to react against environmental influences. It is due to genotypical and peristatic factors. The constitution may be changed if a sufficiently strong peristatic factor produces a permanent change in the reaction susceptibility. Such factors are generally of environmental origin and affect the organism during the more sensitive periods of development—for instance, the embryonal period. Prematurity may be regarded as a peristatic factor having a deteriorating effect on the condition.

WALLGREN, Göteborg, Sweden.

THE PHYSICAL AGE OF CHILDREN AND THE IMPORTANCE OF GIVING DUE CONSIDERATION TO IT IN COMPETITIONS INVOLVING PHYSICAL ACTIVITY. A. BRUUSGAARD, Nord. med. tidskr. **15**:7 (Jan. 1) 1938.

Children who are not satisfactorily developed physically lose interest in physical training as early as the age of 14 or 15. Physical age is a much better basis for the classification of children for physical training and sports. Physical age is determined in the following way: chronologic age $\times$ 2 + weight age + height age $\div$ 4. Children belonging to the same physical age group are very well harmonized in bodily development and physical strength.

WALLGREN, Göteborg, Sweden.

OXYGEN TENSION OF THE BODY. L. J. DELBAERE, Nederl. tijdschr. v. geneesk. **83**:154 (Jan. 14) 1939.

The method first described by Campbell and later by Meyer and Reinhold for determining the subcutaneous oxygen tension by means of an air bubble introduced under the skin was improved so that the gas analysis could be carried out as early as one hour after the introduction of the air. The values found, even those found for the same person, showed wide variations. The significance of these fluctuations is discussed. Most of the patients suffering from heart failure had lowered concentrations, but not all. No abnormal values were found for subjects with arterial hypertension. Patients with pseudoexophthalmic goiter were found to have increased concentrations. Patients with hypertension had values that were about normal.

VAN CREVELD, Amsterdam, Netherlands.

# Society Transactions

## NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

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*May 11, 1939*

OSTEOMYELITIS AND ARTHRITIS DUE TO SALMONELLA SUIPESTIFER IN A MONTH OLD INFANT. DR. JOHN A. WASHINGTON.

An infant who had experienced an unexplained short febrile attack at 1 one week and again at 3 weeks of age had a swelling of the left shoulder at the age of 1 month. At this time he was afebrile and had a white blood cell count of 19,000. Roentgen examination showed osteomyelitis of the upper part of the humerus.

Pus, from which Salmonella suipestifer (group II) was cultured, was aspirated from the joint on three occasions. The infection subsided without surgical drainage. The bacillus was recovered also from the urine but not from the stool or from the blood. The mother's serum agglutinated strongly the organism obtained from the patient. The mother had had no symptoms of an infection either before or after delivery.

ADDISON'S DISEASE IN A BOY TWELVE YEARS OF AGE. DR. GEORGE J. GINANDES.

A case of a 12 year old boy with Addison's disease is presented. The data that suggested the diagnosis were as follows: a history of exposure to a tuberculous father, progressive asthenia and emaciation, a pigmentation of the skin and mucous membranes, a blood pressure of 64 systolic and 42 diastolic, a basal metabolism of — 33 per cent, a positive tuberculin test, the finding of microcardia when roentgen examination was made, and a dramatic response to the administration of dextrose and sodium chloride on the boy's admission to the hospital.

The findings which clinched the diagnosis included the roentgen demonstration of areas of calcification in the region of the adrenals, and the determination of a low sodium content of the blood (114.7 milliequivalents per liter) and a high potassium content (6.9 milliequivalents per liter).

The patient was placed on the diet suggested by Wilder, low in potassium and high in sodium and vitamins, and he showed clinical improvement. Because of several crises, however, the daily administration of adrenal cortex extract was added.

The patient has been maintained on this regimen for about one year and shows sustained improvement. He has gained weight and has a normal blood pressure and a normal amount of blood sodium and potassium.

Desoxycorticosterone acetate will be tried in the near future.

PNEUMOCOCCIC MENINGITIS TREATED WITH SULFAPYRIDINE. DR. IRVING WEINSTOCK.

A single case of pneumococcic meningitis with septicemia, metastatic panophthalmitis and rheumatic heart disease fatal to a 6 year old girl is presented. Extremely large doses of sulfapyridine were administered, 0.4 Gm. per kilogram of body weight daily for eight weeks. The concentration in the blood was not

estimated, because of the lack of facilities. Tests of spinal fluid were always positive for the type IV pneumococcus except for a period of seven days, when in addition to the sulfapyridine, type IV antipneumococcus serum was given. At the end of the sixth week, after the child had received a total of 252 Gm. of sulfapyridine, a bone marrow puncture was performed, and the marrow was found to be normal. No apparent deleterious effects occurred from the massive doses. The function of the kidneys was not impaired. The beneficial effects noted were: minimal meningeal signs, markedly good clinical condition and prolongation of the girl's life.

VACCINIFORM ERUPTION. DR. IRVING POSNER.

On March 24, 1939, a 21 month old boy with a history of a rash of ten days' duration was first admitted to the New York Post-Graduate Medical School and Hospital.

On March 13 the child seemed slightly flushed and feverish, and the following day blisters were noticed on the left thigh, over an area which had been covered by eczema. The child continued to be feverish, and the blisters spread to the hips, wrists and arms. From March 18 to the time of his admission, the temperature varied from 103 to 105 F. There had been no new lesions for the two days previous to his admission. Vomiting had occurred once during the present illness, and there had been no other symptoms. Treatment had consisted of the application of restraints, solution of aluminum acetate N. F., petrolatum and oil.

*Past History.*—The patient has had an infantile eczema since the age of 3 months, which has been present almost constantly despite numerous forms of therapy and dietary restrictions. In the present diet only fish, eggs and chicken are excluded.

The past history otherwise is irrelevant except for immunoprophylaxis. The child received antidiphtheria injections at the age of 6 months with no untoward reaction.

At this point mention should be made of the significant and interesting fact that a 4 year old sibling was vaccinated for smallpox on Feb. 22, 1939, nineteen days before the onset of the present illness in the patient. The sister's lesion ran a typical course and was always covered, the dressings being occasionally moistened by a slight discharge. Although there was no known contact with the lesion, the children did play together.

*Physical Examination.*—The results of physical examination were essentially negative except for the skin. There were one hundred and seventy-four discrete lesions with confluence and plaquelike formation over the thighs and the wrists. The face was entirely clear, but there were numerous lesions on the fingers, and a few of them formed paronychiae.

*Course.*—Wet dressings of solution of aluminum acetate N. F. were continually applied for two days and changed to dressings of a 1:8,000 solution of potassium permanganate thereafter. The child's temperature continued between 101 and 104 F. for eleven days and returned to normal by irregular lysis. No new lesions were observed.

Convalescence was uneventful except for a mild infection of the upper respiratory tract with a rise in temperature for a few days. The vaccinia lesions resolved with residual areas of slightly raised erythema, and the eczema returned in a rather mild form. The child was discharged on the twenty-seventh day in the hospital.

RUPTURE OF THE STOMACH IN THE NEWBORN. DR. ABRAHAM TOW.

The birth of the boy and his family history were normal. The weight at birth was 8 pounds 4 ounces (3,743 Gm.). The child progressed normally until the fifth day (weight, 8 pounds 7 ounces [3,828 Gm.]), when he vomited his 10 a. m. feeding. During the course of the day his abdomen became progressively dis-

tended, and he became more listless. He also vomited his 2 p. m. feeding. When the boy was seen at 4 p. m. his abdomen was markedly distended but soft and flaccid. The temperature was normal. Rectal irrigation gave negative results. The child grew rapidly worse and when seen again an hour later was in a state of shock. A fluid wave could then be elicited. A diagnosis of peritonitis due to a ruptured viscus was made, and roentgenograms were taken. They revealed air in the peritoneal cavity, so much air, in fact, that it looked as if the patient had been given a pneumoperitoneum. In the erect position a distinct fluid level was also evident. An operation was performed, and this revealed a rupture about an inch long in the cardiac end of the stomach on the posterior surface along the greater curvature. The usual supportive measures were administered, and the patient grew progressively better. However, on the fifth postoperative day, the upper portion of the wound opened, with evisceration of some intestinal contents. The boy was returned to the operating room, and it was then found that there had been no healing at the original site of the rupture and that the gastric contents were still leaking out. The rent was resutured, and closure was made in the usual way. However, bleeding from the pedicle of the spleen occurred, and this could be controlled only by a splenectomy. The patient died twelve hours later.

This case brings the total found in the literature to 15. A similar case was reported from this clinic in 1938. A review of these cases reveals the fact that lesions in the cardiac end of the stomach are more tears than the cigaret-burn-like lesions resulting from perforation of a gastric ulcer. Various possibilities as to the causation of the rupture were considered, but it was felt that a congenital defect in the stomach wall itself must be present before this rupture can take place.

A distended abdomen growing progressively worse, with or without signs of toxemia, but with evidence of shock, should lead one to suspect peritonitis due to a ruptured viscus. Roentgenograms revealing air in the peritoneal cavity confirm the diagnosis.

PROGRESSIVE MYOSITIS OSSIFICANS (PROGRESSIVE OSSIFYING FASCIAL HYPERPLASIA). DR. D. J. MCCUNE.

Progressive myositis ossificans is a developmental disease characterized by metaplastic ossification of the intramuscular and intermuscular connective tissue, as well as of the fascial, tendinous and aponeurotic structures of the body. In the great majority of patients the onset of pathologic ossification commences during childhood and progresses during the period normally occupied by the growth of the skeleton. The final result is an elaborate system of extraskeletal bone that seriously handicaps physical activity.

The disease is clearly genetic in origin. Hereditary cases have been reported. The patients frequently exhibit associated anomalies of development; of these the most consistent are microdactylia, achondroplastic deformities of the thumbs and great toes and a species of metaphyseal exostoses indistinguishable from those observed in hereditary deforming chondrodysplasia. Extensive microscopic studies have demonstrated that the first step in the process of pathologic ossification is a sudden metaplastic swelling of connective tissue; the tissue then undergoes ossification, either directly, or indirectly through the intermediary formation of cartilage. This process of ossification expresses itself clinically in bouts characterized by the sudden appearance of subcutaneous tumors which may simulate abscesses and neoplasms.

Although reports have appeared claiming successful treatment with decalcifying agents and roentgen rays, it is the contemporary censensus that all therapy is valueless. Surgical intervention is apt to aggravate the process locally.

The case reported is that of an 11 year old white girl who exhibited nodular masses in her neck when she was 4 years of age. Biopsy of a nodule resulted in a histologic diagnosis of neurofibromatosis. The significance of the presence of extraskeletal bone and of several exostoses was not recognized, and the presence of hallux valgus was ignored. Roentgen treatment was given over a period of

years. Despite this, the disease progressed in a characteristic manner with episodes in which subcutaneous masses appeared, remained a short time and then disappeared, to be followed by new foci of pathologic ossification. The correct diagnosis was made by the chance discovery of Uehlinger's monograph (Uehlinger, E.: Myositis ossificans progressiva, *Ergebn. d. med. Strahlenforsch.* **7**:175, 1936). In another, almost identical case, microscopic examination of biopsy material from the back resulted in a diagnosis of fibrosarcoma. The correct diagnosis did not become apparent until the child had been submitted to unnecessary roentgen treatment for several years.

A Case of Projectile Vomiting. Dr. Frank S. Cross.

M. L., a white girl aged 2 months, was admitted to Willard Parker Hospital on Aug. 21, 1938, with a history of projectile vomiting, a marked loss of weight of one month's duration and cough with whoop of one week's duration. A sister had died at 3 weeks of age after persistent projectile vomiting.

Physical examination revealed an acutely ill, malnourished infant, very pale and markedly dehydrated, with sunken fontanels and very poor tissue turgor. There was a marked loss of subcutaneous fat. The lips and tongue were dry. There was slight cyanosis of the lips and the nail beds. A mass about the size of an olive could be palpated deep in the right hypochondrium. Distinct peristaltic waves could be seen passing from the left side of the abdomen to the right side in the region of the pylorus. Otherwise, physical examination revealed nothing significant. The child had a paroxysmal cough with whoop. She had projectile vomiting within a few minutes after each feeding. Her emesis had little or no relation to her cough, as she would vomit without a preceding coughing spell. She was constipated, having had no stools for the three days preceding her admission. After admission she had a bowel movement every second or third day, consisting of a small, dark brown stool. Examination of the stool revealed no occult blood. The carbon dioxide–combining power was 85 volumes per cent. The diagnosis on the child' admission was pertussis and partial pyloric stenosis.

Surgical intervention was contraindicated, because of the condition of the child and the severity of the pertussis.

The child was placed on a thick gruel formula, 3 or 4 tablespoonfuls of which she was given every three or four hours. Phenobarbital, ¼ grain (0.015 Gm.) by mouth, and atropine, $\frac{3}{1000}$ grain (0.2 mg.) by hypodermic injection, were given fifteen minutes before each feeding. Ascorbic acid, 100 mg., and viosterol, 10 drops, were given daily. Fluids were pushed vigorously by means of hypodermoclysis and rectal drips. Three series of blood transfusions were given.

Three weeks after the child's admission the abdominal tumor was no longer palpable, and ten days later the visible peristaltic waves were gone. Severe emesis continued for another week or so with occasional spells of projectile vomiting until Jan. 15, 1939. The weight curve was kept practically stationary by means of vigorous parenteral pushing of fluids for the first two months of hospitalization. After this the child began to gain in weight; the gruel feedings and medications were discontinued, and the child was placed on a lactic acid formula of high caloric value. This was modified in accordance with her weight curve, and by January 15 she was on a formula suitable for a normal child of her age. She now had a normal weight for her age. She was discharged on January 30, after two weeks without emesis.

A follow-up report of this child reveals that she is a normal child, without symptoms, and that both her weight curve and her feeding habits are normal for a child of her age.

Report of a Case of Bacillus Influenzae Meningitis with Recovery After the Administration of Sulfapyridine. Dr. Frederick H. Wilke.

A boy 2 years and 9 months of age was admitted to St. Luke's Hospital after having stuck a glass rod in the inner canthus of his right eye one week previously. A large hematoma and a slight abrasion of the conjunctiva had resulted.

The mother stated that three days previous to the child's admission he had vomited all his food but that his temperature had been normal; the second day vomiting stopped, and fluids were taken fairly well; the third morning his neck seemed stiff, but his temperature remained normal. On the day of his admission the stiffness of the neck increased steadily, and the temperature suddenly spiked to 104.1 F.

Examination on his admission showed the right eye to be discolored throughout both lids, but the cornea was clear, and no pathologic condition of the globe was noted. External strabismus was also noted. The patient's neck was very stiff, being able to be flexed only about 15 degrees. The boy had bilateral Brudzinski, Babinski and Kernig reflexes, and his knee jerks, although extremely hyperactive, were equal. His entire body was extremely hyperesthetic; he seemed drowsy and irritable, resented movement and kept his knees flexed.

Roentgen examination of the chest showed normal structures; examination of the blood showed: hemoglobin, 70 per cent; red cells, 3.5; leukocytes, 24,000, with 94 per cent polymorphonuclear leukocytes and 6 per cent lymphocytes. A slightly cloudy fluid under almost normal pressure was obtained by a spinal tap, and 15 cc. of antimeningococcus serum was given. A direct smear showed gram-negative bacilli.

After treatment with 0.5 Gm. of sulfapyridine every four hours was instituted, the patient's temperature fell to 98 F. The next day the right eyeball seemed exophthalmic, and the surrounding tissues were swollen, which was reported by the ophthalmologist to indicate a subperiosteal hematoma with no trauma to the orbit. This condition improved daily. Although daily spinal taps were cloudy, no growth was obtained after the day of the child's admission, and the administration of sulfapyridine was discontinued on the seventh day.

The board of health reported Bacillus influenzae in the spinal fluid sent for diagnosis, and this was confirmed by the laboratory at the hospital.

The percentage of hemoglobin dropped to 48, but the red cell count stayed the same; the leukocyte count fell to 8,500, and the blood culture was negative throughout. Two weeks after his admission the patient appeared in normal health and was discharged from the hospital, but one week later his symptoms recurred. He was readmitted to the hospital, and examination revealed the periorbital tissues to be indurated again and showed marked signs of meningeal irritation. A spinal tap again showed cloudy fluid under low pressure, with 540 cells, of which 68 per cent were polymorphonuclear leukocytes and 32 per cent were lymphocytes. The butyric reaction for globulin was 3 plus. Sulfapyridine was again administered, and the temperature promptly fell to normal and remained so; the ocular symptoms immediately subsided. Three months after the onset of the symptoms, the patient was without fever and seemed entirely normal.

This is an extremely interesting case because of the good response to the administration of sulfapyridine, which held the disease in check until the second attack. As an incision was not made at the site of the injury, material for culture was not obtained in order to ascertain if the inner canthus of the right eye could have been the portal of entry for the bacilli.

# News and Comment

## GENERAL NEWS

The following physicians were certified by the American Board of Pediatrics after the examinations in Cincinnati on November 14 and 15:

Marion Leroy Ainsworth, Columbus, Ohio; Philip L. Aries, Chicago; William James Ball, Charleston, S. C.; Ruth Berrey, Birmingham, Ala.; Mercer Blanchard, Columbus, Ga.; Olga Bonke Booher, Indianapolis; David John Bradley, Cincinnati; Charles Pugh Brown, Norfolk, Va.; Clyde Dummer, Cincinnati; J. Gilbert Eblen, Knoxville, Tenn.; Lena Stafford Enright, Findlay, Ohio; Seymour Fisher, Normal, Ill.; Wilbur Jerome Fisher, Buffalo; Thomas G. Folsom, Huntington, W. Va.; Hugh Mason Foster, Toledo, Ohio; Michael Leo Furcolow, Washington, D. C.; John Leo Gedgoud, Chicago; Clarence E. Gilmore, Paris, Texas; Edward A. Hagmann, Billings, Mont.; L. J. Halpern, Chicago; James Mace Harkey, Boston (formerly of Chicago); Barbara Ann Hewell, Cincinnati; Benjamin Ervin Hodge, Clarksburg, W. Va.; Stanley V. Laub, Detroit; Margaret A. Limper, Louisville, Ky.; Emanuel Shalit Lippman, Minneapolis; Sol Londe, St. Louis; Kenneth C. Macpherson, Detroit; Meyer B. Marks, Miami, Fla.; William Taylor Maxson, Lexington, Ky.; Masters H. Moore, Tyler, Texas; Daniel J. Pachman, Chicago; J. Cyril Peterson, Nashville, Tenn.; William M. Petty, Pittsburgh; Samuel X. Radbill, Philadelphia; Frederick Walter Rea, Marion, Ohio; Eli Rubens, Chicago; Nelson William Ryan, Cincinnati; M. I. Saberman, Chicago; Thomas Paine Saltiel, Chicago; Kennith Witwen Schmidt, Denver; Louise Friedaricka Schnute, East Lansing, Mich. (formerly of Ann Arbor, Mich.); Abraham B. Schwartz, Milwaukee; H. Vaughn Scott, Fort Wayne, Ind.; Hyman A. Slesinger, Windber, Pa.; Daniel Lesesne Smith Jr., Spartanburg, S. C.; Maurice Acobert Spalding, Milwaukee (formerly of Chicago); James Walker Stirling, Pittsburgh; Jack Ezell Strange, New Orleans; Charles Klaus Stulik, Chicago; Arthur R. Turner, Chicago; Charles Edward Ward, Jackson, Miss.; Thomas S. Weaver, Cincinnati; Hugh Wellmeier, Piqua, Ohio; Warren Elwell Wheeler, Lansing, Mich.; Lynn W. Whelchel, Miami, Fla.; Scott J. Wilkinson, Decatur, Ill., and Carl Edward Zeithaml, Cleveland.

## CORRECTION

In the article entitled "Pneumococcic Pneumonia of Type XIV in Children Treated with Specific Serum" by Drs. Jesse G. M. Bullowa and Morris Gleich, in the January issue (AM. J. DIS. CHILD. **59**:84, 1940), the word "black" in the second line of the legend for chart 2, on page 87, should read "shaded"; in other words, this part of the legend should read: "The shaded columns represent 137 patients who recovered; the black columns represent 23 patients who died." The number "127" in the second line of the paragraph bearing the center head "Duration," immediately above chart 2, should read "137."

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# Notices

## CUMULATED INDEX OF THE AMERICAN JOURNAL OF DISEASES OF CHILDREN

Requests have been received for a twenty year index of the AMERICAN JOURNAL OF DISEASES OF CHILDREN. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $6 per copy; that is, whether one thousand copies could be sold. It will be appreciated if those who are interested in such an index will fill out the accompanying blank and send it to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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**I SHOULD BE WILLING TO SUBSCRIBE TO A CUMULATED INDEX OF THE AMERICAN JOURNAL OF DISEASES OF CHILDREN AT $6.00.**

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# Book Reviews

**Die Bewertung des Röntgenbefundes bei der kindlichen Tuberkulose.** By Dr. Ottokar von Chiari. Price, 4.80 marks. Pp. 44, with 25 illustrations. Stuttgart: Ferdinand Enke, 1939.

In this 44 page review the author summarizes the changes attributable to tuberculosis in the various tissues in children which are discernible by roentgenography. Although it is admitted that the roentgen rays play an extremely important role in the diagnosis of tuberculosis, the author emphasizes the importance of a careful taking of the history, including that of the family, of a physical examination and especially of a tuberculin test for the correct interpretation of the roentgenograms in each case.

After reviewing the normal lung markings, the author presents fifteen excellent plates of the chest, showing various types of changes produced characteristically by tuberculosis. He first illustrates glandular enlargement about the hilus and the perihilar region, and then the various shadows present in the lung fields, including atelectasis and bronchial stenosis. The full significance of calcification in the chest as well as of other pathologic changes cannot be ascertained until the reaction to tuberculin is known. The author discusses cavity formation and miliary distribution, early apical involvement and outspoken pulmonary infiltrations of the adult type and then devotes himself to observations on skeletal tuberculosis in children. He has seven additional plates of the vertebral columns, the long bones and the hip to illustrate the typical changes caused by tuberculosis, but he again emphasizes the importance of other information to help differentiate such conditions as osteomyelitis, syphilis and osteochondritis. He emphasizes also the importance of atrophy of the osseous tissues in tuberculosis of the bones. Regarding tuberculosis in other tissues of the body, such as the cervical lymph glands, the abdomen and the kidney, he believes the roentgenogram has limited value. The book succeeds in presenting a concise and clear picture of the various manifestations of tuberculosis in children from the roentgenologic point of view.

**Functional Disorders of the Foot: Their Diagnosis and Treatment.** By Frank D. Dickson, M.D., F.A.C.S., and Rex L. Diveley, M.D., F.A.C.S. Price, $5. Pp. 305, with 202 illustrations. Philadelphia: J. B. Lippincott Company, 1939.

The authors of this book present their material in a simple manner which encourages one to read. The text can be used by nurses or by orthopedic surgeons, but it will be of the most value to the general practitioner, who sees the majority of patients with disorders of the feet and ought to have a better understanding of the problem. If the general practitioners would read and profit by this book, many of their patients would not drift away to semiprofessional practitioners.

The authors call attention to the fact that disorders of the feet are an economic, social and medical problem. The text develops the subject in chapters from the anatomy and physiology of the bones and musculature to clinical observations of normal and abnormal functions, especially imbalance of the foot. The causative factors of each functional disorder are discussed, and consequently corrective measures are easily understood.

Local and general constitutional factors are considered for correction. The authors explain how the imbalanced foot is changed to a balanced one by a system of exercises, manipulations, shoe alterations and operations. The authors have found that in most of the preadolescent patients and in some of the older group the condition may be corrected by conservative measures.

# Directory of Pediatric Societies*

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
The meeting is postponed to an indefinite date.

American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: New York. Time: June 10-14, 1940.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. J. B. Bilderback, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel Peabody, Memphis, Tenn. Time: Nov. 18-20, 1940.
Region I. Place: Mayflower Hotel, Washington, D. C. Time: April 4-6, 1940.
Region II. Place: Edgewater Gulf Hotel, Edgewater Park, Miss. Time: March 15-16, 1940.
Region IV. Place: Seattle, Wash. Time: May 30-June 1, 1940.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Herbert B. Wilcox, 39 E. 75th St., New York.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop, Pa. Time: May 2-4, 1940.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Daniel C. Darrow, 330 Cedar St., New Haven, Conn.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: Afternoon of May 1 and morning of May 2, 1940.

## SECTIONAL

### Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

### New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

### Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

## STATE

### Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

### Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

### Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. L. H. Muse, 384 Peachtree St. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Business Meeting. Place: Savannah. Time: April 1940.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Oliver L. Stringfield, 1416 Bedford St., Stamford.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. H. William Elghammer, 5307 Hyde Park Blvd., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: Peoria. Time: May 22, 1940.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Phillip C. De Verges, Audubon Bldg., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 220 Physicians and Surgeons Bldg., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 850 Park Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

TEXAS PEDIATRIC SOCIETY

President: Dr. T. A. Tumbleson, 2100 North St., Beaumont.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Dallas. Time: May 15, 1940.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

## LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Secretary: Dr. David Zahn, 2474 Valentine Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St. N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Secretary: Dr. Harry Apfel, 988 Park Pl., Brooklyn, N. Y.
Place: 1313 Bedford Ave., Brooklyn. Time: 9.00 p. m., second Monday of each month, October to March, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave. N. W. Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

### Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. S. F. Morgan, 5630 N. Lake Dr., Milwaukee.
Secretary-Treasurer: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Rustin McIntosh, Babies Hospital, New York.
Secretary: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northwestern Pediatric Society

President: Dr. Roland E. Nutting, 205 W. 2d St., Duluth, Minn.
Secretary-Treasurer: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L.. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Second Friday of each month.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of ech month from September to June.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. E. Earl Moody, 829 S. Alvarado Ave., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Yark Osterlin, Central Michigan Children's Clinic, Traverse City, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Time: Nov. 15-16, 1940.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (NEW YORK)

President: Dr. M. Bernard Brahdy, 531 E. Lincoln Ave., Mount Vernon.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Ave., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October. December, February and April.